Request Jan [illegible]

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SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Jennifer Kim Examiner #: 77469 Date: 10/4/02
Art Unit: 1617 Phone Number 30 8-2232 Serial Number: 10/044531
Mail Box and Bldg/Room Location: ~~2B19~~ 2D17 Results Format Preferred (circle): PAPER DISK E-MAIL
~~2B19~~

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Use of central cannabinoid receptor antagonists in the preparation of drugs

Inventors (please provide full names): Jeanne Mavuani; Philippe Soubrie

Earliest Priority Filing Date: 1/28/98

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

1) Please provide ~~a~~ Therapeutic uses of formula (II).

2) Please provide registry # of active agent in claim 22. & therapeutic use

3) Please provide Therapeutic uses of formula III in claim 23 and ~~claim~~ formula IV in claim 24, + formula V.

4) Please provide registry # + therapeutic use of ~~claim~~ active agent in claim 26.

Please THX,

* P.S. Please separate each search. (ie. number them 1 – 4 as requested.) THX,

Jennifer.

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher:	NA Sequence (#)		STN	
Searcher Phone #:	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)		Questel/Orbit	
Date Searcher Picked Up:	Bibliographic		Dr.Link	
Date Completed:	Litigation		Lexis/Nexis	
Searcher Prep & Review Time:	Fulltext		Sequence Systems	
Clerical Prep Time:	Patent Family		WWW/Internet	
Online Time:	Other		Other (specify)	

PTO-1590 (8-01)

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STRUCTURE FILE UPDATES:   11 OCT 2002  HIGHEST RN 460983-61-3
DICTIONARY FILE UPDATES:  11 OCT 2002  HIGHEST RN 460983-61-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
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Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can l11

L11  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   168273-06-1  REGISTRY
CN   1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-
     methyl-N-1-piperidinyl- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Rimonabant
CN   SR 141716
FS   3D CONCORD
MF   C22 H21 Cl3 N4 O
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, CA, CAPLUS, CASREACT, CIN, DRUGNL,
       DRUGPAT, DRUGUPDATES, PROMT, TOXCENTER, USPATFULL
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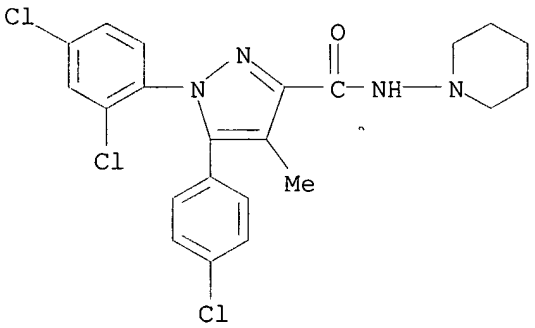

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

              58 REFERENCES IN FILE CA (1962 TO DATE)
               1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
              58 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE   1:  137:150071
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REFERENCE 2: 137:119520

REFERENCE 3: 137:103401

REFERENCE 4: 137:98994

REFERENCE 5: 137:20325

REFERENCE 6: 137:580

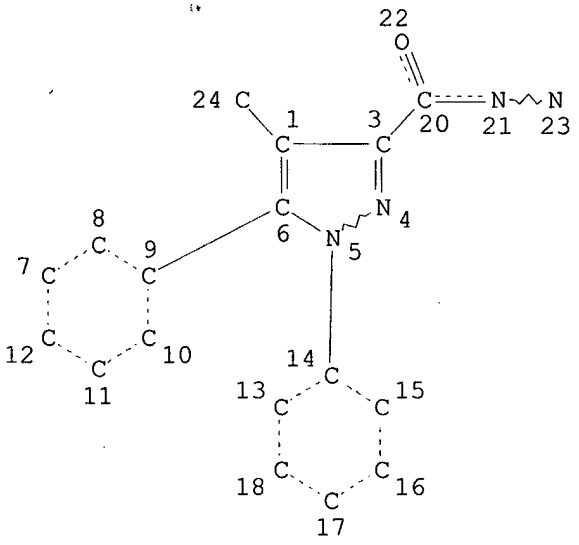
REFERENCE 7: 136:395817

REFERENCE 8: 136:350113

REFERENCE 9: 136:304109

REFERENCE 10: 136:274665

=> d sta que l16
L15 STR



NODE ATTRIBUTES:
NSPEC IS RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L16 103 SEA FILE=REGISTRY SSS FUL L15

100.0% PROCESSED 337 ITERATIONS 103 ANSWERS
SEARCH TIME: 00.00.01

=> d his

(FILE 'HOME' ENTERED AT 09:12:17 ON 13 OCT 2002)

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                E MARUANI J/AU
L1           152 S E3-E5
                E SOUBRIE P/AU
L2           215 S E3-E8
                E SANOFI/PA,CS
L3          1921 S E2,E3,E4
L4          1921 S SANOFI?/PA,CS
                E SYNTHELABO/PA,CS
L5          2057 S SYNTHELAB?/PA,CS
L6            97 S L1,L2 AND L3-L5
                E FR97-870/PA,CS
                E FR97-870/AP,PRN
L7             1 S E3,E4
                E WO98-FR154/AP,PRN
L8             1 S E3,E4
                E US6344474/PN
L9             1 S E3
L10            1 S L1-L6 AND L7-L9
                SEL RN

     FILE 'REGISTRY' ENTERED AT 09:15:36 ON 13 OCT 2002
L11            1 S E1
L12            7 S 168273-06-1/CRN
L13              STR
L14            5 S L13
L15              STR L13
L16          103 S L15 FUL
                SAV L16 JKIM44531/A
L17           95 S L16 NOT L11,L12

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L18            0 S L11 OR L12 OR L17

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L19          226 S L11 OR L12
L20          119 S RIMONABANT OR SR141716 OR SR()(141716 OR 141 716)
L21          608 S SR141716# OR SR()(141716# OR 141 716#)
L22          618 S L19-L21
L23           25 S L17
L24          622 S L22,L23
L25           58 S L11
L26          119 S SR141716 OR SR()(141716 OR 141 716)
L27          130 S L25,L26
L28          492 S L24 NOT L27
L29          362 S L1,L2 NOT L10

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L30          SEL L29 1- RN :     558 TERMS
                SET SMARTSELECT OFF

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L33            7 S E3 AND (46.150.18 AND 591.49.51)/RID
L34            1 S L33 AND 2S
L35            1 S L33 AND 2R
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L36           1 S L34 AND L35
                SEL RN
L37           1 S E1/CRN
L38           1 S L32,L37
L39           7 S L32-L37 NOT L38
                SEL RN
L40           7 S E3-E8/CRN NOT L38
L41           2 S L36,L38
L42          13 S L33,L40 NOT L41

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L45          78 S L43,L44
L46          10 S L42
L47          82 S L45,L46
L48          44 S L27 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L49         164 S L28 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L50           0 S L48 AND L49
L51         170 S L12
L52           6 S L28,L51 AND L27
L53           4 S L52 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L54          80 S L51 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L55          44 S L48,L53
L56          44 S L55 AND L1-L10,L19-L29,L48-L55
L57          46 S L11(L)(THU OR BAC)/RL
L58         146 S (L12 OR L17)(L)(THU OR BAC)/RL
L59          24 S L56 AND L57,L58
L60           4 S L55 AND 63/SC
L61           0 S L55 AND 63/SX
L62          36 S L55 AND 1/SC,SX
L63          24 S L59,L60
L64          16 S L62 NOT L63
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L65           1 S E9-E11 AND L64
L66          25 S L63,L65 AND L1-L10,L19-L29,L48-L65

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FILE LAST UPDATED: 11 Oct 2002  (20021011/ED)

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=> d l66 bib abs hitrn retable tot

L66 ANSWER 1 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:38046 HCAPLUS
DN 130:218189
TI Modulation of CB1 cannabinoid receptor functions after a long-term exposure to agonist or inverse agonist in the Chinese hamster ovary cell expression system
AU Rinaldi-Carmona, Murielle; Le Duigou, Anne; Oustric, Didier; Barth, Francis; Bouaboula, Monsif; Carayon, Pierre; Casellas, Pierre; Le Fur, Gerard
CS **Sanofi Recherche, Montpellier, 34184, Fr.**
SO Journal of Pharmacology and Experimental Therapeutics (**1998**), 287(3), 1038-1047
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB We have investigated the adaptive changes of the human central cannabinoid receptor (CB1) stably expressed in Chinese hamster ovary cells (CHO-CB1), after agonist (CP 55,940) or selective CB1 inverse agonist (**SR 141716**) treatment. CB1 receptor d. and affinity const. as measured by binding assays with both tritiated ligands remained essentially unchanged after varying period exposure of CHO-CB1 cells (from 30 min to 72 h) to satg. concns. of CP 55,940 or **SR 141716**. However, using a C-myc-tagged version of the CB1 receptor, FACS anal. and confocal microscopy studies on CB1 expression indicated that the agonist promoted a disappearance of cell surface receptor although inverse agonist increased its cell surface d. Taken together these results suggest that (1) agonist induces internalization of the receptor into a cellular compartment that would be still accessible to both the hydrophobic ligands CP 55,940 or **SR 141716**; (2) inverse-agonist promotes externalization of the receptor from an intracellular preexisting pool to the cell surface. In parallel, we also investigated the assocd. effects of CP 55,940 and **SR 141716** on CB1 receptor-coupled second messengers. We showed that pre-exposure of cells to CP 55,940 induced a rapid desensitization of the CB1 to the agonist response. The ability of CP 55,940 to inhibit the forskolin-stimulated adenylyl cyclase and to activate the mitogen-activated protein kinase activity was dramatically reduced. By striking contrast, **SR 141716** pretreatment of CHO-CB1 cells not only had no significant effect on the potency of CP 55,940 to inhibit the forskolin-stimulated adenylyl cyclase but also induced a significant enhancement of the CP 55,940 ability to stimulate the mitogen-activated protein kinase activity. These results suggest that the modulation of the no. of cell surface receptor could lead to functional desensitization or sensitization of the CB1 receptors.
IT **168273-06-1, SR 141716**
RL: **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inverse agonist; modulation of CB1 cannabinoid receptor functions after a long-term exposure to agonist or inverse agonist in the Chinese hamster ovary cell expression system)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anderson, N	1990	343	651	Nature	HCAPLUS

Attramadal, H	1992	267	17882	J Biol Chem	HCAPLUS
Barker, E	1994	269	11687	J Biol Chem	HCAPLUS
Barker, E	1993	44	725	Mol Pharmacol	HCAPLUS
Benovic, J	1990	30	3S	Br J Pharmacol	HCAPLUS
Blaukat, A	1996	271	32366	J Biol Chem	HCAPLUS
Bouaboula, M	1995	312	637	Biochem J	HCAPLUS
Bouaboula, M	1996	237	704	Eur J Biochem	HCAPLUS
Bouaboula, M	1993	214	173	Eur J Biol Chem	HCAPLUS
Bouaboula, M	1995	270	13973	J Biol Chem	HCAPLUS
Bouaboula, M	1997	272	22330	J Biol Chem	HCAPLUS
Chun, M	1994	91	11728	Proc Natl Acad Sci U	HCAPLUS
Creese, I	1981	21	357	Annu Rev Pharm Tox	HCAPLUS
Derocq, J	1995	369	177	FEBS Lett	HCAPLUS
Devane, W	1992	258	1946	Science	HCAPLUS
Fan, F	1996	706	13	Brain Res	HCAPLUS
Fan, F	1994	271	1383	J Pharmacol Exp Ter	HCAPLUS
Felder, C	1995	48	443	Mol Pharmacol	HCAPLUS
Fride, E	1995	697	83	Brain Res	HCAPLUS
Galiegue, S	1995	232	54	Eur J Biochem	HCAPLUS
Gerard, C	1991	279	129	Biochem J	HCAPLUS
Grady, E	1995	270	4603	J Biol Chem	HCAPLUS
Grady, E	1995	6	509	Mol Biol Cell	HCAPLUS
Graham, F	1973	54	536	Virology	HCAPLUS
Howlett, A	1984	26	532	Mol Pharmacol	HCAPLUS
Kaminski, N	1992	42	736	Mol Pharmacol	HCAPLUS
Kenakin, T	1996	48	413	Pharmacol Rev	HCAPLUS
Koenig, J	1994	269	17174	J Biol Chem	HCAPLUS
Labrecque, J	1995	48	150	Mol Pharmacol	HCAPLUS
Landsman, R	1997	334	R1	Eur J Pharmacol	HCAPLUS
Lefkowitz, R	1993	14	304	TIPS	
Lohse, M	1990	248	1547	Science	HCAPLUS
Mac Ewan, D	1996	50	1479	Mol Pharmacol	HCAPLUS
Mackie, K	1992	89	3825	Proc Natl Acad Sci U	HCAPLUS
Massi, P	1997	58	73	Pharmacol Biochem Be	HCAPLUS
Matsuda, L	1990	346	561	Nature	HCAPLUS
Milligan, G	1995	16	10	Trends Pharmacol Sci	HCAPLUS
Miloux, B	1994	149	341	Gene	HCAPLUS
Munro, S	1993	365	61	Nature	HCAPLUS
Onorato, J	1991	30	5118	Biochemistry	HCAPLUS
Oviedo, A	1993	616	293	Brain Res	HCAPLUS
Ozcelebi, F	1996	271	3750	J Biol Chem	HCAPLUS
Pak, Y	1996	50	1214	Mol Pharmacol	HCAPLUS
Palczewski, K	1989	28	8764	Biochemistry	HCAPLUS
Pertwee, R	1993	110	1483	Br J Pharmacol	HCAPLUS
Pertwee, R	1991		231	The Biological Bases	HCAPLUS
Rinaldi-Carmona, M	1994	350	240	FEBS Lett	HCAPLUS
Rinaldi-Carmona, M	1996	278	871	J Pharmacol Exp Ther	HCAPLUS
Rinaldi-Carmona, M	1995	56	1941	Life Sci	HCAPLUS
Rodriguez De Fonseca, F	1994	47	33	Pharmacol Biochem Be	MEDLINE
Rubino, T	1994	5	2493	NeuroReport	HCAPLUS
Scarpace, P	1982	223	327	J Pharmacol Exp Ther	HCAPLUS
Shire, D	1995	270	3726	J Biol Chem	HCAPLUS
Shire, D	1996	271	6941	J Biol Chem	HCAPLUS
Slipetz, D	1995	48	352	Mol Pharmacol	HCAPLUS
Thomas, R	1992	89	4490	Proc Natl Acad Sci U	HCAPLUS
Tietz, E	1986	236	282	J Pharmacol Exp Ther	
Twitchell, W	1997	78	43	J Neurophysiol	HCAPLUS
Von Zastrow, M	1992	267	3530	J Biol Chem	HCAPLUS
Werling, L	1989	86	6393	Proc Natl Acad Sci U	HCAPLUS
Westlake, T	1994	63	637	Neurosciences	HCAPLUS

L66 ANSWER 2 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:727905 HCAPLUS

DN 130:90442
TI Effects of cannabinoids on prolactin and gonadotrophin secretion: involvement of changes in hypothalamic .gamma.-aminobutyric acid (GABA) inputs
AU De Miguel, Rosario; Romero, Julian; Munoz, Raul M.; Garcia-Gil, Lucia; Gonzalez, Sara; Villanua, Maria A.; Makriyannis, Alexandros; Ramos, Jose A.; Fernandez-Ruiz, J. Javier
CS DEPARTMENT OF BIOCHEMISTRY, FACULTY OF MEDICINE, COMPLUTENSE UNIVERSITY, MADRID, 28040, Spain
SO Biochemical Pharmacology (**1998**), 56(10), 1331-1338
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
AB CB1 cannabinoid receptors are located in hypothalamic nuclei and their activation alters several hypothalamic neurotransmitters resulting in, among other things, decreased prolactin (PRL) and LH secretion from the anterior pituitary gland. In the present study, we addressed two related objectives to further explore this complex regulation. First, we examd. whether changes in .gamma.-aminobutyric acid (GABA) and/or dopamine (DA) inputs in the medial basal hypothalamus might occur in parallel to the effects resulting from the activation of CB1 receptors on PRL and gonadotrophin secretion in male rats. Thus, the acute administration of (-)-.DELTA.9-tetrahydrocannabinol (.DELTA.9-THC) produced, as expected, a marked decrease in plasma PRL and LH levels, with no changes in FSH levels. This was paralleled by an increase in the contents of GABA, but not of DA, in the medial basal hypothalamus and, to a lesser extent, in the anterior pituitary gland. The co-administration of .DELTA.9-THC and **SR141716**, a specific antagonist for CB1 receptors, attenuated both PRL and LH decrease and GABA increase, thus asserting the involvement of the activation of CB1 receptors in these effects. As a second objective, we tested whether the prolonged activation of these receptors might induce tolerance with regard to the decrease in PRL and LH release, and whether this potential tolerance might be related to changes in CB1-receptor binding and/or mRNA expression. The chronic administration of R-methanandamide (AM356), a more stable analog of anandamide, the putative endogenous cannabinoid ligand, produced a marked decrease in plasma PRL and LH levels, with no changes in FSH. The decreases were of similar magnitude to those caused by a single injection of this cannabimimetic ligand, thus suggesting the absence of tolerance. In parallel, the anal. of CB1-receptor binding and mRNA expression in several hypothalamic structures proved that the acute or chronic administration of AM356 did not affect either the binding or the synthesis of these receptors. In summary, the activation of CB1 receptors in hypothalamic nuclei produced the expected decrease in PRL and LH secretion, an effect which might be related to an increase in GABAergic activity in the hypothalamus-anterior pituitary axis. The prolonged activation of these receptors for five days did not elicit tolerance in terms of an attenuation in the magnitude of the decrease in PRL and LH, and, accordingly, did not alter CB1-receptor binding and mRNA levels in the hypothalamic nuclei examd.
IT **168273-06-1, SR141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(effects of cannabinoids on prolactin and gonadotrophin secretion and involvement of changes in hypothalamic GABA inputs)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Abadji, V	1994	37	1889	J Med Chem	HCAPLUS
Bonnin, A	1994	48	1387	Biochem Pharmacol	HCAPLUS
Bonnin, A	1994	16	305	Neuroendocrine Lett	HCAPLUS
Bonnin, A	1993	58	280	Neuroendocrinology	HCAPLUS

Dalterio, S	1986	8	345	Neurobehav Toxicol T	HCAPLUS
de Fonseca, F	1991	43	713	Neuroscience	
de Fonseca, F	1992	42	269	Pharmacol Biochem Be	
Devane, W	1992	258	1946	Science	HCAPLUS
Esquifino, A	1994	60	581	Neuroendocrinology	HCAPLUS
Esquifino, A	1995	208	397	Proc Soc Exp Biol Me	HCAPLUS
Fernandez-Ruiz, J	1997	53	1919	Biochem Pharmacol	HCAPLUS
Fernandez-Ruiz, J	1992		119	Marihuana/Cannabinoi	HCAPLUS
Fernandez-Ruiz, J	1992	14	349	Neuroendocrine Lett	HCAPLUS
Herkenham, M	1991	11	563	J Neurosci	HCAPLUS
Howlett, A	1990	13	420	Trends Neurosci	HCAPLUS
Hughes, C	1981	109	876	Endocrinology	HCAPLUS
Jansen, E	1992	575	93	Brain Res	HCAPLUS
Kramer, J	1978	103	452	Endocrinology	HCAPLUS
Lynn, A	1994	268	1612	J Pharmacol Exp Ther	HCAPLUS
Mailleux, P	1992	48	655	Neuroscience	HCAPLUS
Muller, E	1989	21	75	Pharmacol Res	MEDLINE
Murphy, L	1990	2	73	Biochemistry and Phy	
Murphy, L	1994	16	1	Neuroendocrine Lett	HCAPLUS
Murphy, L	1990	52	316	Neuroendocrinology	HCAPLUS
Murphy, L	1991	40	603	Pharmacol Biochem Be	HCAPLUS
Nicoletti, F	1985	44	1217	J Neurochem	HCAPLUS
Oviedo, A	1993	616	293	Brain Res	HCAPLUS
Paxinos, G	1986			The rat brain in ste	
Puder, M	1985	59	213	Exp Brain Res	HCAPLUS
Racagni, G	1982	31	823	Life Sci	HCAPLUS
Rinaldi-Carmona, M	1994	350	240	FEBS Lett	HCAPLUS
Romero, J	1997	46	100	Brain Res Mol Brain	HCAPLUS
Romero, J	1998	62	351	Life Sci	HCAPLUS
Romero, J	1998	63	351	Life Sci	HCAPLUS
Romero, J	1994	16	159	Neuroendocrine Lett	HCAPLUS
Romero, J	1998	84	1075	Neuroscience	HCAPLUS
Rubino, T	1994	5	2493	Neuroreport	HCAPLUS
Schimchowitsch, S	1991	83	575	Exp Brain Res	MEDLINE
Sim, L	1996	15	8057	J Neurosci	
Smith, S	1994	652	228	J Chromatography	HCAPLUS
Sugita, S	1992	134	207	Neurosci Lett	HCAPLUS
Tal, J	1983	273	179	Brain Res	HCAPLUS
Tuomisto, J	1985	37	249	Pharmacol Rev	HCAPLUS
Wagner, B	1994	659	194	Brain Res	
Wenger, T	1997	237	724	Biochem Biophys Res	HCAPLUS
Wenger, T	1994	16	295	Neuroendocrine Lett	

L66 ANSWER 3 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:682119 HCAPLUS
DN 129:293903
TI Pharmaceutical composition for oral administration of a n-piperidino-3-pyrazolecarboxamide derivatives, its salts and their solvates
IN Abramovici, Bernard; Condamine, Christian; Gromenil, Jean-Claude
PA **SANOFI, Fr.**
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9843636	A1	19981008	WO 1998-FR631	19980327 <--

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

FR 2761266	A1	19981002	FR 1997-3835	19970328	<--
FR 2761266	B1	19990702			
ZA 9802609	A	19980930	ZA 1998-2609	19980327	<--
AU 9870527	A1	19981022	AU 1998-70527	19980327	<--
AU 740486	B2	20011108			
EP 969832	A1	20000112	EP 1998-917259	19980327	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI					
BR 9808429	A	20000523	BR 1998-8429	19980327	<--
AT 202703	E	20010715	AT 1998-917259	19980327	<--
JP 2001517224	T2	20011002	JP 1998-541241	19980327	<--
ES 2161049	T3	20011116	ES 1998-917259	19980327	<--
PRAI FR 1997-3835	A	19970328	<--		
WO 1998-FR631	W	19980327			

AB Pharmaceutical compns. for oral administration contain 0.5 % to 20 % of N-piperidino-5- (4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (I) in microcryst. form and pharmaceutical vehicles. The compns. are formulated by wet granulation. A pharmaceutical capsule contained I 1 mg, starch 51, lactose monohydrate 103.33, povidone K30 4.3, CM-cellulose sodium 8.5, sodium lauryl sulfate 0.17, and magnesium stearate 1.7 mg.

IT **168273-06-1**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(pharmaceutical compn. for oral administration of piperidinopyrazolecarboxamide derivs., its salts and their solvates)

L66 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:682118 HCAPLUS
DN 129:293902
TI Pharmaceutical composition for oral administration of a N-piperidino-3-pyrazolecarboxamide derivative, its salts and their solvates
IN Gautier, Jean-Claude; Marrier, Jean-Marie
PA **SANOFI, Fr.**
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 9843635	A1	19981008	WO 1998-FR630	19980327	<--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
FR 2761265	A1	19981002	FR 1997-3834	19970328	<--
FR 2761265	B1	19990702			
AU 9870526	A1	19981022	AU 1998-70526	19980327	<--
PRAI FR 1997-3834		19970328	<--		
WO 1998-FR630		19980327			

AB Pharmaceutical compns. contg. 0.5 % to 8 % of N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (I) and 1.5 % to 5 % of Poloxamer F127, formulated in a macrogoglyceride. A capsule contained I 10, Gelucire 44-14 235, and Poloxamer F127 5 mg.

IT **168273-06-1**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)

(1995 J. Pain Symptom. Manage. 10(2), 89-97. J. Palliat. Care (1994) 10(1) 14-18)

(pharmaceutical compn. for oral administration of piperidinopyrazolecarboxamide derivs.)

L66 ANSWER 5 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:635123 HCAPLUS
DN 129:339820
TI Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity
AU Shen, Maoxing; Thayer, Stanley A.
CS Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN, 55455, USA
SO Molecular Pharmacology (**1998**), 54(3), 459-462
CODEN: MOPMA3; ISSN: 0026-895X
PB Williams & Wilkins
DT Journal
LA English
AB Cannabinoid receptor agonists act presynaptically to inhibit the release of glutamate. Because other drugs with this action are known to reduce excitotoxicity, the authors tested several cannabimimetics in a model of synaptically mediated neuronal death. Redn. of the extracellular Mg2+ concn. to 0.1 mM evoked a repetitive pattern of intracellular Ca2+ concn. ([Ca2+]i) spiking that, when maintained for 24 h, resulted in significant neuronal death. The [Ca2+]i spiking and cell death in this model result from excessive activation of N-methyl-D-aspartate receptors, as indicated by the inhibition of both [Ca2+]i spiking and neuronal death by the N-methyl-D-aspartate receptor antagonist CGS19755 (10 .mu.M). The cannabimimetic drug Win55212-2 (100 nM) completely blocked [Ca2+]i spiking and prevented neuronal death induced by low extracellular Mg2+ concns. These effects on [Ca2+]i spiking and viability were stereoselective and were prevented by the CB1 receptor antagonist **SR141716** (100 nM). The partial agonist CP55940 (100 nM) also afforded significant protection from excitotoxicity. Cannabimimetic drugs did not protect cells from the direct application of glutamate (30 .mu.M). These data suggest that cannabimimetic drugs may slow the progression of neurodegenerative diseases.
IT **168273-06-1, SR141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity)

L66 ANSWER 6 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:623584 HCAPLUS
DN 129:298324
TI .DELTA.9-Tetrahydrocannabinol induces apoptosis in C6 glioma cells
AU Sanchez, Cristina; Galve-Roperh, Ismael; Canova, Cecile; Brachet, Philippe; Guzman, Manuel
CS School of Biology, Department of Biochemistry and Molecular Biology I, Complutense University, Madrid, 28040, Spain
SO FEBS Letters (**1998**), 436(1), 6-10
CODEN: FEBLAL; ISSN: 0014-5793
PB Elsevier Science B.V.
DT Journal
LA English
AB .DELTA.9-Tetrahydrocannabinol (THC), the major active component of marijuana, induced apoptosis in C6.9 glioma cells, as detd. by DNA fragmentation and loss of plasma membrane asymmetry. THC stimulated sphingomyelin hydrolysis in C6.9 glioma cells. THC and N-acetylsphingosine, a cell-permeable ceramide analog, induced apoptosis in several transformed neural cells but not in primary astrocytes or neurons. Although glioma C6.9 cells expressed the CB1 cannabinoid receptor, neither THC-induced apoptosis nor THC-induced sphingomyelin

breakdown were prevented by **SR141716**, a specific antagonist of that receptor. Results thus show that THC-induced apoptosis in glioma C6.9 cells may rely on a CB1 receptor-independent stimulation of sphingomyelin breakdown.

IT **168273-06-1, SR141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(.DELTA.9-Tetrahydrocannabinol induces apoptosis in C6 glioma cells)

L66 ANSWER 7 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:608544 HCAPLUS
DN 129:235654
TI Movement of a test substance within a membranous system
IN Melchior, Donald L.; Makriyannis, Alexandros
PA University of Massachusetts, USA; University of Connecticut
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9837920	A1	19980903	WO 1998-US3823	19980227 <--
	W: AU, CA, JP, KR				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9866704	A1	19980918	AU 1998-66704	19980227 <--
PRAI	US 1997-795948		19970228 <--		
	WO 1998-US3823		19980227		

AB A method is disclosed for detg. the rate with which a test mol. assocs. with or accumulates in a membrane, by forming a membranous system that contains lipid mols. in assocn. with a reporter mol., applying the test mol. to the system, and measuring the signal generated by the reporter mol. The tests are performed to det. pharmaceuticals mode of action and whether they can be safely and efficiently delivered to the site of action. An example is given for prepn. of fluorosomes contg. the reporter mol. diphenylhexatriene and phosphatidylcholine as the lipid.

IT **168273-06-1**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(movement of a test substance within a membranous system)

L66 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:551124 HCAPLUS
DN 129:270516
TI Cannabinoids decrease excitatory synaptic transmission and impair long-term depression in rat cerebellar Purkinje cells
AU Levenes, Carole; Daniel, Herve; **Soubrie, Philippe**; Crepel, Francis
CS Laboratoire de Neurobiologie et Neuropharmacologie du Developpement, Paris, 75005, Fr.
SO Journal of Physiology (Cambridge, United Kingdom) (**1998**), 510(3), 867-879
CODEN: JPHYA7; ISSN: 0022-3751
PB Cambridge University Press
DT Journal
LA English
AB CB-1 cannabinoid receptors are strongly expressed in the mol. layer of the cerebellar cortex. We analyzed, in patch-clamped Purkinje cells (PCs) in rat cerebellar slices, the effect of the selective CB-1 agonists WIN55,212-2 and CP55,940 and of the selective CB-1 antagonist **SR141716**-A on excitatory synaptic transmission and synaptic

plasticity. Bath application of both agonists markedly depressed parallel fiber (PF) excitatory postsynaptic currents (EPSC)s. This effect was reversed by **SR141716**-A. Responses of PCs to ionophoretic application of glutamate were not affected by WIN55,212-2. The coeff. of variation and the paired-pulse facilitation of these PF-mediated EPSCs increased in the presence of WIN55,212-2. WIN55,212-2 decreased the frequency of miniature EPSCs and of asynchronous synaptic events evoked in the presence of Sr in the bath, but did not affect their amplitude. WIN55,212-2 did not change the excitability of PFs. WIN55,212-2 impaired long-term depression induced by pairing protocols in PCs. This effect was antagonized by **SR141716**-A. The same impairment of LTD was produced by 2-chloroadenosine, a compd. that decreases the probability of release of glutamate at PF-PC synapses. It was demonstrated that cannabinoids inhibit synaptic transmission at PF-PC synapses by decreasing the probability of release of glutamate, and thereby impair LTD. These 2 effects might represent a plausible cellular mechanism underlying cerebellar dysfunction caused by cannabinoids.

IT **158681-13-1, SR 141716A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(CB-1 cannabinoid receptor antagonist **SR141716**-A effect on the excitatory synaptic transmission in cerebellar Purkinje cells)

L66 ANSWER 9 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:527208 HCAPLUS
DN 129:144865
TI Use of central cannabinoid receptor antagonists for regulating appetence
IN **Maruani, Jeanne; Soubrie, Philippe**
PA **Sanofi, Fr.**
SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	WO 9832441	A1	19980730		WO 1998-FR154	19980128	<--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM						
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG						
	FR 2758723	A1	19980731		FR 1997-870	19970128	<--
	FR 2758723	B1	19990423				
	ZA 9800691	A	19980805		ZA 1998-691	19980128	<--
	AU 9862193	A1	19980818		AU 1998-62193	19980128	<--
	EP 969835	A1	20000112		EP 1998-904238	19980128	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI						
	BR 9806801	A	20000516		BR 1998-6801	19980128	<--
	JP 2001501971	T2	20010213		JP 1998-531693	19980128	<--
	TW 450808	B	20010821		TW 1998-87101128	19980217	<--
	NO 9903634	A	19990927		NO 1999-3634	19990727	<--
	LV 12354	B	20000220		LV 1999-114	19990727	<--
	US 6344474	B1	20020205		US 1999-341764	19990819	<--
	US 2002128302	A1	20020912		US 2002-44531	20020111	<--
PRAI	FR 1997-870	A	19970128	<--			
	WO 1998-FR154	W	19980128	<--			
	US 1999-341764	A3	19990819				

OS MARPAT 129:144865

AB The use of a central cannabinoid receptor antagonist (Markush structure given), on its own or combined with a compd. for regulating metabolic disorders, in particular a .beta.3-adrenergic receptor agonist, for prepg. medicines useful for treating appetence disorders is disclosed. N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (**SR 141716**) at a dose of 0.3 mg/kg reduced the consumption of sucrose and alc. in guinea pigs. A capsule contained micronized **SR 141716** 1.00, corn starch 51.00, lactose monohydrate 103.33, polyvidone 4.30, sodium lauryl sulfate 0.17, sodium CM-cellulose 8.50, and magnesium stearate 1.70 mg.

IT **168273-06-1, SR 141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(use of central cannabinoid receptor antagonists for regulating appetence)

L66 ANSWER 10 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:489016 HCAPLUS
DN 129:211620
TI Appetite suppression and weight loss after the cannabinoid antagonist **SR 141716**
AU Colombo, Giancarlo; Agabio, Roberta; Diaz, Giacomo; Lobina, Carla; Reali, Roberta; Gessa, Gian Luigi
CS C.N.R. Center for Neuropharmacology, Cagliari, Italy
SO Life Sciences (1998), 63(8), PL113-PL117
CODEN: LIFSAK; ISSN: 0024-3205
PB Elsevier Science Inc.
DT Journal
LA English
AB The effect of the cannabinoid CB1 receptor antagonist, **SR 141716**, on food intake and body wt. was assessed in adult, non-obese Wistar rats. The daily administration of **SR 141716** (2.5 and 10 mg/kg; i.p.) reduced dose-dependently both food intake and body wt. Tolerance to the anorectic effect developed within 5 days; in contrast, body wt. in **SR 141716**-treated rats remained markedly below that of vehicle-treated rats throughout the entire treatment period (14 days). The results suggest that brain cannabinoid receptors are involved in the regulation of appetite and body wt.

IT **168273-06-1, SR 141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(appetite suppression and wt. loss after cannabinoid antagonist **SR 141716** in relation to role of brain cannabinoid antagonist in appetite regulation and development of tolerance)

L66 ANSWER 11 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:319380 HCAPLUS
DN 129:62852
TI Evaluation of cannabinoid receptor agonists and antagonists using the guanosine-5'-O-(3-[35S]thio)-triphosphate binding assay in rat cerebellar membranes
AU Griffin, Graeme; Atkinson, Peter J.; Showalter, Vincent M.; Martin, Billy R.; Abood, Mary E.
CS Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, USA
SO Journal of Pharmacology and Experimental Therapeutics (1998), 285(2), 553-560
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English

AB Cannabinoid receptors are members of the superfamily of G protein-coupled receptors. Their activation has previously been shown to stimulate guanosine 5'-O-(3-[35S]thio)-triphosphate ([35S]GTP.gamma.S) binding in a range of brain regions using both membrane prepns. and autoradiog. This study evaluates the activities of structurally diverse cannabinoid receptor ligands in the GTP.gamma.S binding assay, comparing the relationship between receptor binding and activation and also examg. efficacy differences between compds. Using rat cerebellar membrane prepns., the effects of GDP concn. on GTP.gamma.S binding and the activities of a range of cannabinoid receptor ligands, including the CB1 selective antagonist **SR141716A**, were investigated. GDP concn. was found to have differing effects on cannabinoid-stimulated [35S]GTP.gamma.S binding depending on the nature of the agonist used. The stimulation produced by high efficacy compds., such as CP 55,940 and WIN 55212-2, was increased by raising the GDP concn., but that of a low efficacy agonist, (-)-.DELTA.-tetrahydrocannabinol, was decreased. Of the cannabinoid compds. tested, a wide range of potencies (EC50) and levels of maximal stimulation (Emax) were obsd. These ranged from CP 55,244 (Emax of 165, 148-183%, and an EC50 of 0.47, 0.22-0.96, nM) through (-)-.DELTA.-tetrahydrocannabinol, cannabinol and anandamide, which produced no concn.-dependent stimulation of [35S]GTP.gamma.S binding under the same conditions. **SR141716A** competitively antagonized all the agonists against which it was tested, providing equil. dissocn. consts. (Kd values) in the sub-nanomolar range (0.06-0.40 nM), implicating a CB1 receptor mediated response. These results provide a more detailed characterization of the cannabinoid-stimulated [35S]GTP.gamma.S binding assay than has previously been reported.

IT **168273-06-1, SR141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(evaluation of cannabinoid receptor agonists and antagonists using the guanosine-5'-O-(3-thio)triphosphate binding assay)

L66 ANSWER 12 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:290653 HCAPLUS
DN 129:64245
TI Reduction of voluntary ethanol intake in ethanol-preferring sP rats by the cannabinoid antagonist **SR-141716**
AU Colombo, Giancarlo; Agabio, Roberta; Fa, Mauro; Guano, Lorenza; Lobina, Carla; Loche, Antonella; Reali, Roberta; Gessa, Gian Luigi
CS C.N.R. Center Neuropharmacology, University Cagliari, Cagliari, I-09124, Italy
SO Alcohol and Alcoholism (Oxford) (1998), 33(2), 126-130
CODEN: ALALDD; ISSN: 0735-0414
PB Oxford University Press
DT Journal
LA English
AB The present study assessed the efficacy of the cannabinoid CB1 receptor antagonist, **SR-141716**, in reducing voluntary ethanol intake in selectively bred Sardinian alc.-preferring (sP) rats. Ethanol (10%, vol./vol.) and food were available in daily 4 h scheduled access periods; water was present 24 h/day. The acute administration of a 2.5 and a 5 mg/kg dose of **SR-141716** selectively reduced ethanol intake, whereas a 10 mg/kg dose of **SR-141716** reduced to a similar extent both ethanol and food intake. These results suggest that the cannabinoid CB1 receptor is involved in the mediation of the ethanol-reinforcing effects in sP rats.

IT **168273-06-1, SR-141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(redn. of voluntary ethanol intake in ethanol-preferring sP rats by the cannabinoid antagonist **SR-141716**)

L66 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:281777 HCAPLUS
DN 129:76332
TI **SR 141716**, a CB1 cannabinoid receptor antagonist, selectively reduces sweet food intake in marmoset
AU Simiand, J.; Keane, M.; Keane, P. E.; **Soubrie, P.**
CS **Sanofi Recherche, Toulouse, 31036, Fr.**
SO Behavioural Pharmacology (1998), 9(2), 179-181
CODEN: BPHAEL; ISSN: 0955-8810
PB Rapid Science Ltd.
DT Journal
LA English
AB **SR 141716** (1 and 3 mg/kg p.o.), a selective central (CB1) cannabinoid receptor antagonist, selectively reduced feeding of a very highly palatable cane-sugar mixt. in marmosets. In contrast, std. primate pellet intake was not modified at the lower dose, but was slightly increased (+29%; $p < 0.01$) by the higher dose of **SR 141716**. These results are in agreement with the hypothesis that endogenous cannabinoid systems are involved in the modulation of the appetitive value of food.
IT **168273-06-1, SR 141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(**SR 141716**, a CB1 cannabinoid receptor antagonist, selectively reduces sweet food intake in marmoset)

L66 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN **1998:200760** HCAPLUS
DN **128:316761**
TI Cannabinoid receptor agonists and antagonists
AU Barth, Francis
CS **Sanofi Recherche, Montpellier, 34184, Fr.**
SO Expert Opinion on Therapeutic Patents (1998), 8(3), 301-313
CODEN: EOTPEG; ISSN: 1354-3776
PB Ashley Publications
DT Journal; General Review
LA English
AB A review, with 111 refs. Following the discovery of two distinct cannabinoid receptors (CB1 and CB2) in the early 1990s, the medicinal chem. of cannabinoids has seen renewed interest. In the last decade, at least three entirely new chem. series were shown to bind to cannabinoid receptors: the aminoalkylindoles developed by Sterling (WIN 55212-2 analogs), the fatty acid derivs. derived from the endogenous ligand anandamide, and Sanofi's diaryl pyrazoles. Moreover, other compds., such as benzofurans (Lilly) or substituted arom. amide derivs. (Japan Tobacco) that also bind to cannabinoid receptor have recently been disclosed in the patent literature. In terms of pharmacol. profile, the major advances of the last five years are the emergence of selective CB2 agonists (Merck, Sanofi) with potential applications as immunomodulants and the development of the first selective CB1 antagonist **SR 141716**, followed recently by the first CB2 antagonist SR 144528. Turning these newly discovered pharmacol. tools into useful drugs remains the challenge for research in coming years.

L66 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:46949 HCAPLUS
DN 128:149875
TI Cannabinoid CB1 receptor-mediated inhibition of noradrenaline release in the human and guinea-pig hippocampus. [Erratum to document cited in CA128:10525]
AU Schlicker, E.; Timm, J.; Zentner, J.; Gothert, M.
CS Institut fur Pharmakologie und Toxikologie, Universitat Bonn, Bonn, D-53113, Germany

SO Naunyn-Schmiedeberg's Archives of Pharmacology (1998), 357(2), 190
CODEN: NSAPCC; ISSN: 0028-1298
PB Springer-Verlag
DT Journal
LA English
AB Due to unfortunate errors, the concns. of Ca2+ and K+ in the 9th and 10th line of the Abstr. and the concn. of Ca2+ in the 17th line of the right column on p.584 are incorrect. It should have read "mM" instead of ".mu.M".
IT **168273-06-1, SR 141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(cannabinoid CB1 receptor-mediated inhibition of noradrenaline release in human and guinea pig brain (Erratum))

L66 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:693969 HCAPLUS
DN 128:10525
TI Cannabinoid CB1 receptor-mediated inhibition of noradrenaline release in the human and guinea pig hippocampus
AU Schlicker, E.; Timm, J.; Zentner, J.; Gothert, M.
CS Institut fur Pharmakologie und Toxikologie, Universitat Bonn, Reuterstrasse 2b, Bonn, D-53113, Germany
SO Naunyn-Schmiedeberg's Archives of Pharmacology (1997), 356(5), 583-589
CODEN: NSAPCC; ISSN: 0028-1298
PB Springer
DT Journal
LA English
AB We examd. the question of whether cannabinoid receptors modulating noradrenaline release are detectable in the brain of humans and exptl. animals. For this purpose, hippocampal slices from humans, guinea pigs, rats and mice and cerebellar, cerebrocortical and hypothalamic slices from guinea pigs were incubated with [3H]noradrenaline and then superfused. Tritium overflow was evoked either elec. (0.3 or 1 Hz) or by introduction of Ca2+ (1.3 .mu.M) into Ca2+-free, K+-rich medium (25 .mu.M) contg. tetrodotoxin 1 .mu.M. Furthermore, the cAMP accumulation stimulated by forskolin 10 .mu. M was detd. in guinea pig hippocampal membranes. We used the following drugs: the cannabinoid receptor agonists CP-55,940 and WIN 55,212-2, the inactive S(-)-enantiomer of the latter (WIN 55,212-3) and the CB1 receptor antagonist **SR 141716**. The elec. evoked tritium overflow from guinea pig hippocampal slices was reduced by WIN 55,212-2 (pIC30% 6.5) but not affected by WIN 55,212-3 up to 10 .mu.M. The concn.-response curve of WIN 55,212-2 was shifted to the right by **SR 141716** (0.032 .mu.M) (apparent pA2 8.2), which by itself did not affect the evoked overflow. WIN 55,212-2 (1 .mu.M) also inhibited the Ca2+-evoked tritium overflow in guinea pig hippocampal slices and the elec. evoked overflow in guinea pig cerebellar, cerebrocortical and hypothalamic slices as well as in human hippocampal slices but not in rat and mouse hippocampal slices. **SR 141716** (0.32 .mu.M) markedly attenuated the WIN 55,212-2-induced inhibition in guinea pig and human brain slices. **SR 141716** (0.32 .mu.M) by itself increased the elec. evoked tritium overflow in guinea pig hippocampal slices but failed to do so in slices from the other brain regions of the guinea pig and in human hippocampal slices. The cAMP accumulation stimulated by forskolin was reduced by CP-55,940 and WIN 55,212-2. The concn.-response curve of CP 55,940 was shifted to the right by **SR 141716** (0.1 .mu.M; apparent pA2 8.3), which by itself did not affect cAMP accumulation. In conclusion, cannabinoid receptors of the CB1 subtype occur in the human hippocampus, where they may contribute to the psychotropic effects of cannabis, and in the guinea pig hippocampus, cerebellum, cerebral cortex

and hypothalamus. The CB1 receptor in the guinea pig hippocampus is located presynaptically, is activated by endogenous cannabinoids and may be neg. coupled to adenylyl cyclase.

IT **168273-06-1, SR 141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(cannabinoid CB1 receptor-mediated inhibition of noradrenaline release in human and guinea pig brain)

L66 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:496071 HCAPLUS
DN 127:185723
TI Selective inhibition of sucrose and ethanol intake by **SR 141716**, an antagonist of central cannabinoid (CB1) receptors
AU Arnone, Michele; **Maruani, Jeanne**; Chaperon, Frederique; Thiebot, Marie-Helene; Poncelet, Martine; **Soubrie, Philippe**; Le Fur, Gerard
CS **Sanofi Recherche, Route d'Espagne, Toulouse, F-31000, Fr.**
SO Psychopharmacology (Berlin) (1997), 132(1), 104-106
CODEN: PSCHDL; ISSN: 0033-3158
PB Springer
DT Journal
LA English
AB **SR 141716**, a selective central CB1 cannabinoid receptor antagonist, markedly and selectively reduces sucrose feeding and drinking as well as neuropeptide Y-induced sucrose drinking in rats. **SR 141716** also decreases ethanol consumption in C57BL/6 mice. In contrast, blockade of CB1 receptors only marginally affects regular chow intake or water drinking. The active doses of **SR 141716** (0.3-3 mg/kg) are in the range known to antagonize the characteristic effects induced by cannabinoid receptor agonists. These results suggest for the first time that endogenous cannabinoid systems may modulate the appetitive value of sucrose and ethanol, perhaps by affecting the activity of brain reward systems.

IT **168273-06-1, SR 141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(cannabinoid antagonist **SR 141716** selective inhibition of sucrose and ethanol intake)

L66 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:433633 HCAPLUS
DN 127:55894
TI Stable freeze-dried pharmaceutical formulation containing mannitol and alanine
IN Bouloumie, Colette; Breul, Thierry; Colliere, Laurence; Faure, Philippe
PA **Sanofi, Fr.**; Bouloumie, Colette; Breul, Thierry; Colliere, Laurence; Faure, Philippe
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9717064	A1	19970515	WO 1996-FR1706	19961030 <--

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,

IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

FR 2740686	A1	19970509	FR 1995-13022	19951103	<--
FR 2740686	B1	19980116			
CA 2234140	AA	19970515	CA 1996-2234140	19961030	<--
AU 9674990	A1	19970529	AU 1996-74990	19961030	<--
AU 713383	B2	19991202			
EP 858325	A1	19980819	EP 1996-937367	19961030	<--
EP 858325	B1	20020731			

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI

CN 1203527	A	19981230	CN 1996-198786	19961030	<--
BR 9611367	A	19990223	BR 1996-11367	19961030	<--
JP 11507945	T2	19990713	JP 1996-517912	19961030	<--
CZ 287178	B6	20001011	CZ 1998-1231	19961030	<--
IL 124214	A1	20010128	IL 1996-124214	19961030	<--
RU 2163801	C2	20010310	RU 1998-110638	19961030	<--
AT 221374	E	20020815	AT 1996-937367	19961030	<--
ZA 9609176	A	19980430	ZA 1996-9176	19961031	<--
TW 442295	B	20010623	TW 1996-85114410	19961122	<--
NO 9801967	A	19980630	NO 1998-1967	19980430	<--
US 6284277	B1	20010904	US 1998-66387	19981209	<--
PRAI FR 1995-13022	A	19951103	<--		
WO 1996-FR1706	W	19961030	<--		

AB A pharmaceutically acceptable freeze-dried formulation consisting of an amorphous phase and a cryst. phase and including at least one non-protein active principle is disclosed. The formulation is characterized in that it contains mannitol and alanine in a ratio R of 0.1-1, where R is the wt. of mannitol over the wt. of alanine. A free-dried pharmaceutical contained SR 57746A 0.44, alanine 72.0, mannitol 36.0, citric acid 30.8, and Polysorbate-80 4.0 mg.

IT **168273-06-1**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(stable freeze-dried pharmaceutical formulation contg. mannitol and alanine)

L66 ANSWER 19 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:359669 HCAPLUS
DN 127:75864
TI Atypical location of cannabinoid receptors in white matter areas during rat brain development
AU Romero, J.; Garcia-Palomero, E.; Berrendero, F.; Garcia-Gil, L.; Hernandez, M. L.; Ramos, J. A.; Fernandez-Ruiz, J. J.
CS Inst. Complutense Drogodependencias, Dep. Biochem., Fac. Med., Complutense Univ., Madrid, Spain
SO Synapse (New York) (1997), 26(3), 317-323
CODEN: SYNAET; ISSN: 0887-4476
PB Wiley-Liss
DT Journal
LA English
AB Previous evidence suggest that the endogenous cannabinoid system could merge and be operative early during brain development. In the present study, the authors have explored the distribution of specific binding for cannabinoid receptors in rat brain at gestational day 21 (GD21), postnatal days 5 (PND5) and 30 (PND30), and at adult age (>70 days after birth) by using autoradiog. with [3H]CP-55,940. The results indicated that specific binding for cannabinoid receptors can be detected in the brain of rat fetuses at GD21 in the classic areas that contain these receptors in adulthood-in particular, in the cerebellum and the hippocampus and, to a lesser extent, in the basal ganglia, several limbic structures, and cerebral cortex. The d. of cannabinoid receptors in all these structures increased progressively at all postnatal ages studied until reaching the classical adult values in 70-day-old animals. Interestingly, cannabinoid

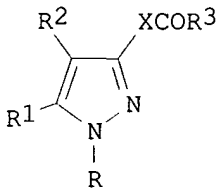
receptor binding can also be detected at GD21 in regions, in which they are scarcely distributed or not located in the adult brain and that have the particularity of all being enriched in neuronal fibers. Among these were the corpus callosum, anterior commissure, stria terminalis, fornix, white matter areas of brainstem, and others. This atypical location was quant. high at GD21, tended to wane at PND5, and practically disappeared PND30 and in adulthood, with the only exception being the anterior commissure, which exhibited a moderate d. for cannabinoid receptors. Moreover, the binding of [3H]CP-55,940 to cannabinoid receptors in the white matter regions at GD21 seems to be functional and involves a GTP-binding protein-mediated mechanism. Thus, the activation of these receptors with an agonist such as WIN-55,212-2 increased the binding of [35S]-guanylyl-5'-O-(.gamma.-thio)-triphosphate, measured by autoradiog., in the corpus callosum and white matter areas of brainstem of fetuses at GD21. This increase was reversed by coincubation of WIN-55,212-2 with **SR141716**, a cannabinoid receptor antagonist. As this antagonist is specific for the cerebral cannabinoid receptor subtype, called CB1, the authors can assert that the signal found for cannabinoid receptor binding in the fetal and early postnatal brain likely corresponds to this receptor subtype. Collectively, all these data suggest that existence of a transient period of the brain development in the rat, around the last days of the fetal period and the first days of postnatal life, in which CB1 receptors appear located in neuronal fiber-enriched areas. During this period, CB1 receptors would be already functional acting through a GTP-binding protein-mediated mechanism. After this transient period, they progressively acquire the pattern of adult distribution. All this accounts for a specific role of the endogenous cannabinoid system in brain development.

IT **168273-06-1, SR141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(atypical location of cannabinoid receptors in white matter areas during rat brain development)

L66 ANSWER 20 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:311258 HCAPLUS
DN 127:5085
TI Pyrazole derivatives as cannabinoid receptor agonists
IN Barth, Francis; Casellas, Pierre; Congy, Christian; Martinez, Serge; Rinaldi, Murielle; Anne-Archard, Gilles
PA **Sanofi, Fr.**
SO U.S., 45 pp., Cont.-in-part of U.S. Ser. No. 168,237, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	US 5624941	A	19970429		US 1994-348881	19941129	<--
	FR 2692575	A1	19931224		FR 1992-7645	19920623	<--
	FR 2692575	B1	19950630				
	FR 2713224	A1	19950609		FR 1993-14444	19931202	<--
	FR 2713224	B1	19960301				
	FR 2713225	A1	19950609		FR 1994-8974	19940720	<--
	FR 2713225	B1	19960301				
	ZA 9409342	A	19951009		ZA 1994-9342	19941124	<--
	JP 2001026541	A2	20010130		JP 2000-238472	19941202	<--
PRAI	FR 1992-7645	A	19920623	<--			
	US 1993-79870	B2	19930623	<--			
	FR 1993-14444	A	19931202	<--			
	US 1993-168237	B2	19931217	<--			
	FR 1994-8974	A	19940720	<--			
	JP 1994-300016	A3	19941202	<--			

OS MARPAT 127:5085
GI



I

AB Title compds. I [R, R1 = (un)substituted Ph; R2 = H, alkyl; R3 = amino, (un)substituted alkyl, cycloalkyl aryl, heterocyclic; X = bond, NR4, CH2NR4; R4 = H, alkyl] were prepd. and have cannabinoid receptor affinity (no data). Thus, 4-ClC6H4COEt was treated with EtO2CCO2Et to give 4-ClC6H4C(OLi):CMeCOCO2Et which was cyclized with 2,4-Cl2C6H3NHNH2 to give I [R = 2,4-Cl2C6H3, R1 = 4-ClC6H4, R2 = Me, X = bond, R3 = OEt]. The ester was hydrozyled to the acid, converted to the chloride, and amidated with 1-aminopiperidine to give I [R = 2,4-Cl2C6H3, R1 = 4-ClC6H4, R2 = Me, X = bond, R3 = piperidinoamino].

IT **168273-06-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of diarylpyrazoles as cannabinoid receptor agonists)

IT **158681-13-1P 169544-42-7P 169544-44-9P**
169544-45-0P 169544-46-1P 190141-47-0P
190141-50-5P 190141-51-6P 190141-52-7P
190141-53-8P 190141-54-9P 190141-55-0P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of diarylpyrazoles as cannabinoid receptor agonists)

L66 ANSWER 21 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:41341 HCAPLUS
DN 126:220668
TI Cannabinoid receptor-mediated inhibition of dopamine release in the retina
AU Schlicker, Eberhard; Timm, Joerg; Goethert, Manfred
CS Institut Pharmakologie Toxikologie, Rheinische Friedrich-Wilhelms-Universitaet, Bonn, D-53113, Germany
SO Naunyn-Schmiedeberg's Archives of Pharmacology (**1996**), 354(6), 791-795
CODEN: NSAPCC; ISSN: 0028-1298
PB Springer
DT Journal
LA English
AB The possible occurrence of cannabinoid (CB) receptors was studied on superfused guinea-pig retinal disks preincubated with [3H]dopamine ([3H]DA) or [3H]noradrenaline ([3H]NA). Tritium overflow was evoked either elec. (3 Hz) or by re-introduction of Ca2+ 1.3 mM after superfusion with Ca2+-free medium contg. K+ 30 mM. The accumulation of [3H]DA and [3H]NA was inhibited by the selective inhibitor of the neuronal dopamine transporter GBR-12909 (pIC50% 7.29 and 7.41, resp.) but not by the selective inhibitor of the neuronal noradrenaline transporter desipramine (1 .mu.M). The elec. or Ca2+-evoked tritium overflow in retinal disks preincubated with [3H]DA or [3H]NA was reduced by the CB receptor agonists P-55,940 and WIN 55,2122 (pIC50% in disks preincubated with [3H]NA, elec. stimulation: 7.03 and 6.70, resp.) but not affected by the inactive S(-)enantiomer of the latter, WIN 55,2123 (up to 10 .mu.M). The concn.-response curve of WIN 55,2122 was shifted to the right by the CB1

receptor antagonist **SR 141716** (apparent pA2: 8.29) which, by itself, increased the evoked overflow. The facilitatory effect of **SR 141716** was not affected by GBR-12909 and the dopamine receptor antagonist haloperidol. In conclusion, the dopaminergic neurons of the guinea-pig retina can be labeled by both [3H]DA and [3H]NA. Transmitter release from the dopaminergic neurons is inhibited by activation of cannabinoid receptors of the CR1 type, which appear to be tonically activated by an endogenous CB receptor ligand.

IT **168273-06-1, SR 141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(cannabinoid receptor-mediated inhibition of dopamine release in retina)

L66 ANSWER 22 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:556840 HCAPLUS
DN 125:265677
TI Improvement of memory in rodents by the selective CB1 cannabinoid receptor antagonist, **SR 141716**
AU Terranova, J. P.; Storme, J. J.; Lafon, N.; Perio, A.; Rinaldi-Carmona, M.; Le Fur, G.; **Soubrie, P.**
CS Montpellier, F-34184, Fr.
SO Psychopharmacology (Berlin) (**1996**), 126(2), 165-172
CODEN: PSCHDL; ISSN: 0033-3158
PB Springer
DT Journal
LA English
AB Social short-term memory in rodents is based on the recognition of a juvenile by an adult conspecific when the juvenile is presented on two successive occasions. Cannabimimetics are claimed to induced memory deficits in both humans and animals. In the brain, they mainly bind to CB1 receptors for which anandamide is a purported endogenous ligand. **SR 141716**, a specific antagonist of CB1 receptors, dose-dependently reverses biochem. and pharmacol. effects of cannabimimetics. More particularly, it antagonizes the inhibition of hippocampal long-term potentiation induced by WIN 55,212-2 and anandamide, and it increases arousal when given alone. The present expts. study the ability of **SR 141716** (from 0.03 to 3 mg/kg SC) to facilitate short-term olfactory memory in the social recognition test in rodents. **SR 141716** improved social recognition in a long intertrial paradigm with a threshold dose of 0.1 mg/kg SC. At 1 mg/kg, it antagonized the memory disturbance elicited by retroactive inhibition. Scopolamine (0.06 mg/kg IP) partially reversed its memory-enhancing effect. Moreover, **SR 141716** reduced memory deficit in aged rats (0.03-0.1 mg/kg) and mice (0.3-1 mg/kg). As **SR 141716** is not known to exhibit any pharmacol. activity which is not mediated by CB1 receptors, the results strongly support the concept that blockade of CB1 receptors plays an important role in consolidation of short-term memory in rodents and suggest there may be a role for an endogenous cannabinoid agonist tone (anandaminergic) in forgetting.

IT **168273-06-1, SR 141716**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(improvement of memory in rodents by the selective CB1 cannabinoid receptor antagonist **SR 141716**)

L66 ANSWER 23 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:987208 HCAPLUS
DN 124:76310
TI Inhibition of long-term potentiation in rat hippocampal slices by anandamide and WIN55212-2: reversal by **SR141716** A, a selective

antagonist of CB1 cannabinoid receptors
AU Terranova, Jean-Paul; Michaud, Jean-Claude; Le Fur, Gerard; **Soubrie, Philippe**
CS **Sanofi Recherche, Montpellier, F-34184, Fr.**
SO Naunyn-Schmiedeberg's Archives of Pharmacology (**1995**), 352(5), 576-9
CODEN: NSAPCC; ISSN: 0028-1298
PB Springer
DT Journal
LA English
AB It has been reported previously that .DELTA.9-tetrahydrocannabinol and the synthetic cannabinoid agonist HU-210 [(-)-11-OH-.DELTA.8-dimethylheptyltetrahydrocannabinol] prevent long-term potentiation (LTP) induction in rat hippocampal slices. In this study we confirm that both WIN 55212-2 (3 and 10.mu.M), another synthetic cannabinoid agonist, and anandamide (10.mu.M), considered to be the endogenous ligand of cannabinoid receptors, inhibit LTP formation in the Schaffer collateral-CA1 field complex. In addn., we show that **SR141716** A (0.1-10.mu.M), a potent and selective antagonist of CB1 cannabinoid receptors, concn.-dependently reversed the inhibition of LTP induced by both WIN55212-2 and anandamide. These data indicate that cannabinoid receptor agonists inhibit hippocampal LTP formation through CB1 receptor activation and that anandamide could be a candidate for an endogenous neuromessenger involved in memory processes.
IT **158681-13-1**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of long-term potentiation in rat hippocampal slices by anandamide and WIN55212-2 and reversal by CB1 cannabinoid receptor antagonist)

L66 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:887840 HCAPLUS
DN 123:286006
TI Preparation of N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide as a cannabinoid receptor antagonist
IN Barth, Francis; Casellas, Pierre; Congy, Christian; Martinez, Serge; Rinaldi, Murielle; Anne-Archard, Gilles
PA **Sanofi, Fr.**
SO Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 656354	A1	19950607	EP 1994-402717	19941129 <--
EP 656354	B1	19970604		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
FR 2713224	A1	19950609	FR 1993-14444	19931202 <--
FR 2713224	B1	19960301		
FR 2713225	A1	19950609	FR 1994-8974	19940720 <--
FR 2713225	B1	19960301		
IL 111719	A1	19991028	IL 1994-111719	19941121 <--
AU 9478999	A1	19950615	AU 1994-78999	19941123 <--
AU 685518	B2	19980122		
ZA 9409342	A	19951009	ZA 1994-9342	19941124 <--
CA 2136893	AA	19950621	CA 1994-2136893	19941129 <--
AT 154012	E	19970615	AT 1994-402717	19941129 <--
ES 2105575	T3	19971016	ES 1994-402717	19941129 <--
NO 9404625	A	19950606	NO 1994-4625	19941201 <--
CN 1110968	A	19951101	CN 1994-119030	19941201 <--
CN 1047775	B	19991229		

	RU 2141479	C1	19991120	RU 1994-42232	19941201 <--
	PL 180289	B1	20010131	PL 1994-306067	19941201 <--
	FI 9405690	A	19950603	FI 1994-5690	19941202 <--
	HU 71498	A2	19951128	HU 1994-3471	19941202 <--
	HU 218277	B	20000728		
	JP 07309841	A2	19951128	JP 1994-300016	19941202 <--
	JP 3137222	B2	20010219		
	JP 2001026541	A2	20010130	JP 2000-238472	19941202 <--
PRAI	FR 1993-14444	A	19931202 <--		
	FR 1994-8974	A	19940720 <--		
	JP 1994-300016	A3	19941202 <--		

OS CASREACT 123:286006

AB The title compd. (I) was pred. by treating 4-ClC6H4COEt with (Me3Si)2NLi and (CO2Et)2 to give 4-ClC6H4CH(OLi)CHMeCOCO2Et which was cyclocondensed with 2,4-Cl2C6H3NHNH2 and the product sapond. to give 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylic acid which was amidated by 1-aminopiperidine. I had ED50 of 0.4mg/kg orally for antagonism of WIN 5521-2-induced hypothermia in mice.

IT **158681-13-1P 168273-06-1P 169544-42-7P 169544-43-8P 169544-44-9P 169544-45-0P 169544-46-1P**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide as a cannabinoid receptor antagonist)

L66 ANSWER 25 OF 25 HCAPLUS COPYRIGHT 2002 ACS

AN 1995:823081 HCAPLUS

DN 123:228179

TI Preparation of 1,5-diphenyl-3-pyrazolecarboxamide derivatives with cannabinoid receptor affinity

IN Barth, Francis; Casellas, Pierre; Congy, Christian; Martinez, Serge; Rinaldi, Murielle

PA **SANOFI, Fr.**

SO Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW

DT Patent

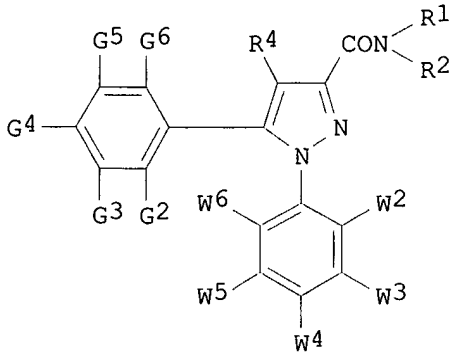
LA French

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 658546	A1	19950621	EP 1994-402890	19941215 <--
	EP 658546	B1	20010523		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	FR 2714057	A1	19950623	FR 1993-15221	19931217 <--
	FR 2714057	B1	19960308		
	ES 2159549	T3	20011016	ES 1994-402890	19941215 <--
	US 5462960	A	19951031	US 1994-357880	19941216 <--
	JP 07324076	A2	19951212	JP 1994-315224	19941219 <--
PRAI	FR 1993-15221	A	19931217 <--		

OS MARPAT 123:228179

GI



I

AB The title compds. [I; g2-g6, W2-W6 = Ph, H, Cl, Br, I, alkyl, alkoxy, CF3, NO2; R1, R4 = H, alkyl; R2 = (un)substituted NH2, (un)substituted ammonium] [e.g., N-(1,2,3,6-tetrahydropyridin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide hydrochloride; m.p. 200.degree. (decompn.)], which have cannabinoid receptor affinity (no data), are prepd.

IT **168272-65-9P 168272-66-0P 168273-09-4P**
168273-10-7P 168273-11-8P 168273-12-9P
168273-13-0P 168273-14-1P 168273-15-2P
168273-16-3P 168273-17-4P 168273-18-5P
168273-19-6P 168273-20-9P 168273-21-0P
168273-22-1P 168273-23-2P 168273-24-3P
168273-25-4P 168273-26-5P 168273-27-6P
168273-28-7P 168273-29-8P 168273-30-1P
168273-31-2P 168273-32-3P 168273-33-4P
168273-34-5P 168273-36-7P 168273-37-8P
168273-40-3P 168273-41-4P 168273-42-5P
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 1,5-diphenyl-3-pyrazolecarboxamide derivs. with cannabinoid receptor affinity)

IT **168273-06-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 1,5-diphenyl-3-pyrazolecarboxamide derivs. with cannabinoid receptor affinity from)

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Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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STRUCTURE FILE UPDATES: 11 OCT 2002 HIGHEST RN 460983-61-3
DICTIONARY FILE UPDATES: 11 OCT 2002 HIGHEST RN 460983-61-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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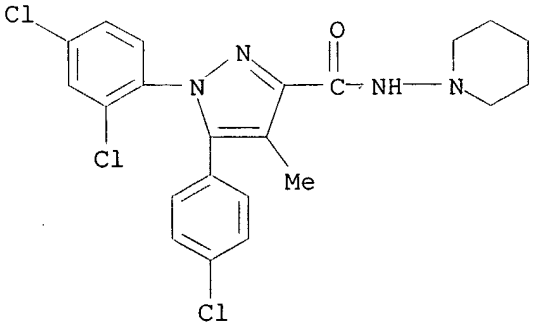
L12 ANSWER 1 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 190141-47-0 REGISTRY
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, (2E)-2-butenedioate (2:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, (E)-2-butenedioate (2:1)
FS STEREOSEARCH
MF C22 H21 Cl3 N4 O . 1/2 C4 H4 O4
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

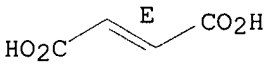
CRN 168273-06-1
CMF C22 H21 Cl3 N4 O



CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



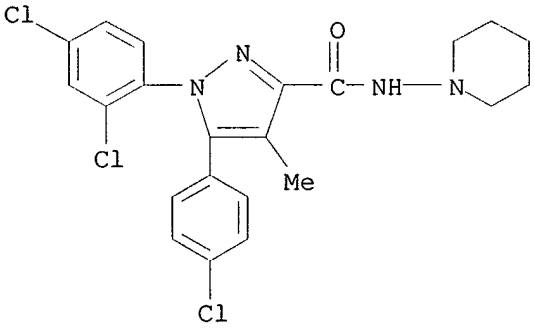
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 127:5085

L12 ANSWER 2 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 169544-46-1 REGISTRY
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, phosphate (1:1) (9CI) (CA INDEX NAME)
MF C22 H21 Cl3 N4 O . H3 O4 P
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

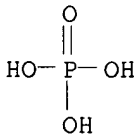
CM 1

CRN 168273-06-1
CMF C22 H21 Cl3 N4 O



CM 2

CRN 7664-38-2
CMF H3 O4 P



2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

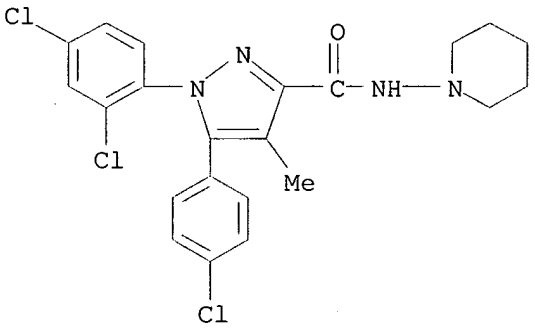
REFERENCE 1: 127:5085

REFERENCE 2: 123:286006

L12 ANSWER 3 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 169544-45-0 REGISTRY
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, mono(4-methylbenzenesulfonate) (9CI) (CA INDEX NAME)
MF C22 H21 Cl3 N4 O . C7 H8 O3 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

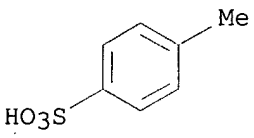
CM 1

CRN 168273-06-1
CMF C22 H21 Cl3 N4 O



CM 2

CRN 104-15-4
CMF C7 H8 O3 S



2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

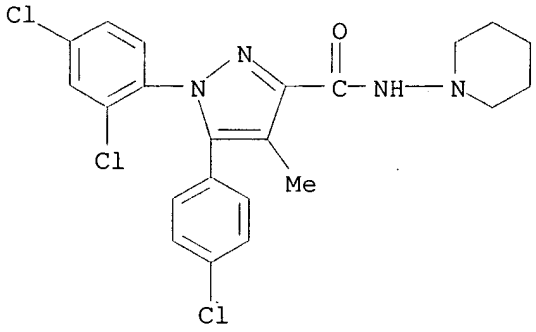
REFERENCE 1: 127:5085

REFERENCE 2: 123:286006

L12 ANSWER 4 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 169544-44-9 REGISTRY
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, sulfate (1:1) (9CI) (CA INDEX NAME)
MF C22 H21 Cl3 N4 O . H2 O4 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

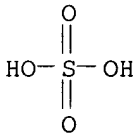
CM 1

CRN 168273-06-1
CMF C22 H21 Cl3 N4 O



CM 2

CRN 7664-93-9
CMF H2 O4 S



2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

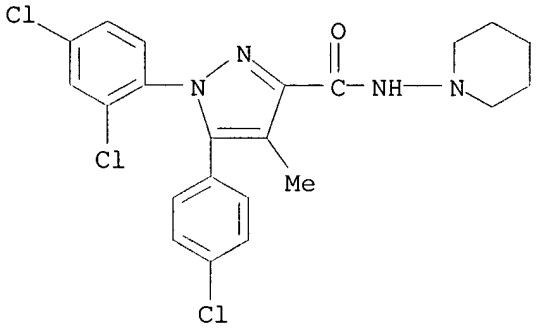
REFERENCE 1: 127:5085

REFERENCE 2: 123:286006

L12 ANSWER 5 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 169544-43-8 REGISTRY
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, (E)-2-butenedioate (1:1)
FS STEREOSEARCH
MF C22 H21 Cl3 N4 O . C4 H4 O4
SR CA
LC STN Files: CA, CAPLUS

CM 1

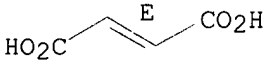
CRN 168273-06-1
CMF C22 H21 Cl3 N4 O



CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



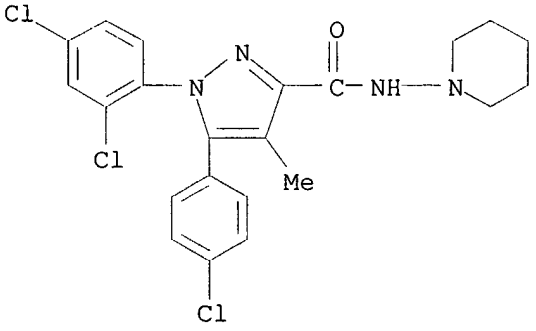
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 123:286006

L12 ANSWER 6 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 169544-42-7 REGISTRY
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, monomethanesulfonate (9CI) (CA INDEX NAME)
MF C22 H21 Cl3 N4 O . C H4 O3 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

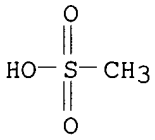
CM 1

CRN 168273-06-1
CMF C22 H21 Cl3 N4 O



CM 2

CRN 75-75-2
CMF C H4 O3 S

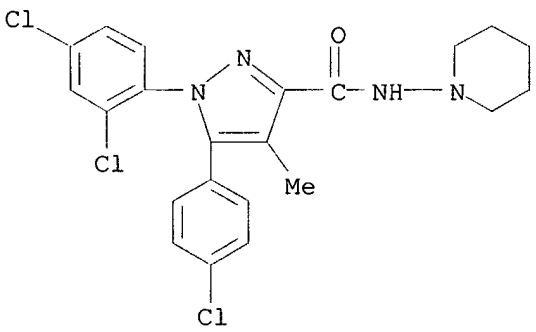


2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 127:5085

REFERENCE 2: 123:286006

L12 ANSWER 7 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 158681-13-1 REGISTRY
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, monohydrochloride (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SR 141716A
MF C22 H21 Cl3 N4 O . Cl H
SR CA
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CEN, EMBASE, MEDLINE, PHAR, PROMT, TOXCENTER, USPATFULL
CRN (168273-06-1)



● HCl

170 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
170 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:179571

REFERENCE 2: 137:164054

REFERENCE 3: 137:135279

REFERENCE 4: 137:134880

REFERENCE 5: 137:30923

REFERENCE 6: 136:395814

REFERENCE 7: 136:350460

REFERENCE 8: 136:273092

REFERENCE 9: 136:226615

REFERENCE 10: 136:129277

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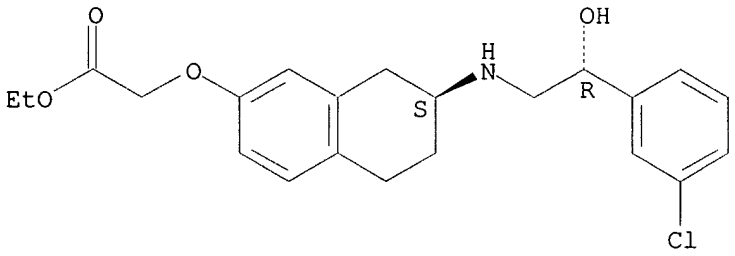
L41 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2002 ACS
RN **121524-09-2** REGISTRY
CN Acetic acid, [[(7S)-7-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride, [R-(R*,S*)]-
OTHER NAMES:
CN SR 58611
CN SR 58611A
FS STEREOSEARCH
MF C22 H26 Cl N O4 . Cl H
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, DDFU, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, MEDLINE, PHAR, PROMT, TOXCENTER, USPATFULL
CRN (121524-08-1)

Absolute stereochemistry.



● HCl

52 REFERENCES IN FILE CA (1962 TO DATE)
52 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:210721

REFERENCE 2: 137:195329

REFERENCE 3: 136:334973

REFERENCE 4: 135:205794

REFERENCE 5: 135:103720

REFERENCE 6: 135:40399

REFERENCE 7: 135:29332

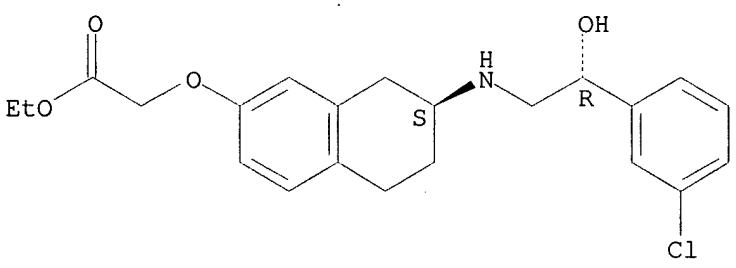
REFERENCE 8: 135:435

REFERENCE 9: 134:126373

REFERENCE 10: 133:344976

L41 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2002 ACS
RN 121524-08-1 REGISTRY
CN **Acetic acid, [[(2S)-7-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, [R-(R*,S*)]-
FS STEREOSEARCH
MF **C22 H26 Cl N O4**
CI COM
SR CA
LC STN Files: ADISINSIGHT, BIOTECHNO, CA, CAPLUS, CASREACT, EMBASE, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9 REFERENCES IN FILE CA (1962 TO DATE)
9 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 127:55894

REFERENCE 2: 126:99317

REFERENCE 3: 125:133456

REFERENCE 4: 122:132788

REFERENCE 5: 122:105454

REFERENCE 6: 121:230444

REFERENCE 7: 120:153732

REFERENCE 8: 115:57179

REFERENCE 9: 111:39023

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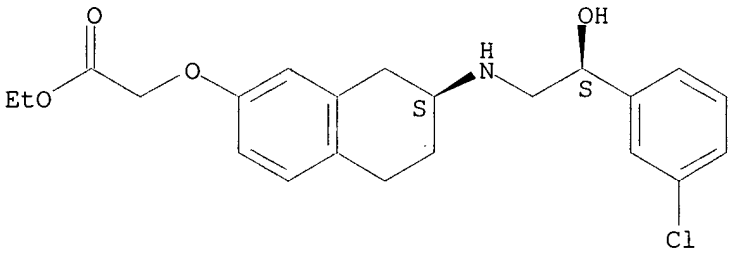
L42 ANSWER 1 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 135025-88-6 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C22 H26 Cl N O4**
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



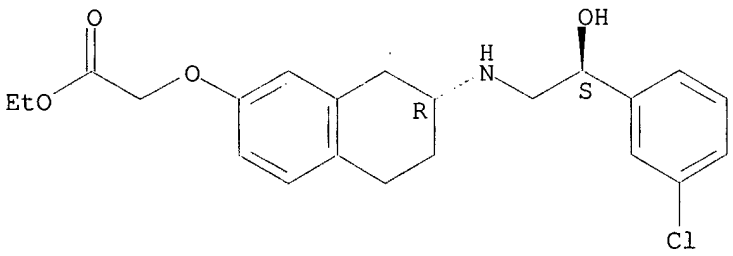
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 115:57179

L42 ANSWER 2 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 135025-87-5 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C22 H26 Cl N O4**
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)

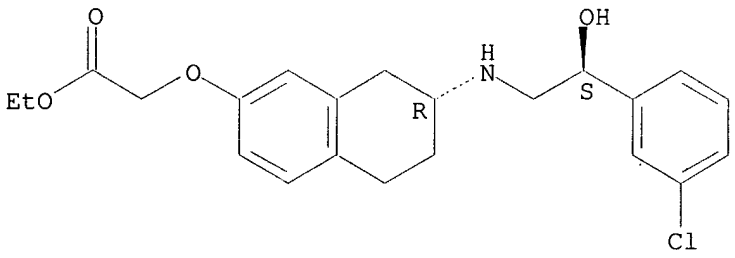
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 117:163882

REFERENCE 2: 115:57179

L42 ANSWER 3 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 129831-97-6 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride, [S-(R*,S*)]-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN SR 58825A
FS STEREOSEARCH
MF C22 H26 Cl N O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS, DDFU, DRUGU, USPATFULL
CRN (135025-87-5)

Absolute stereochemistry.



● HCl

5 REFERENCES IN FILE CA (1962 TO DATE)
5 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 121:230444

REFERENCE 2: 117:185365

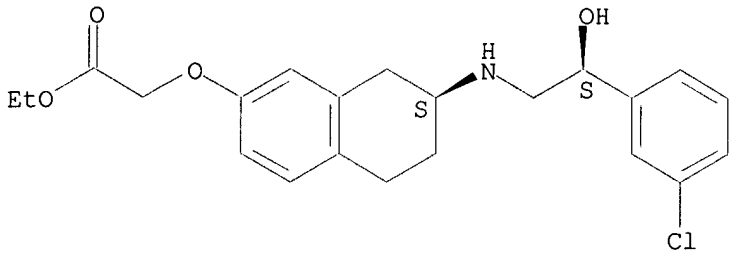
REFERENCE 3: 117:163882

REFERENCE 4: 115:57179

REFERENCE 5: 113:165225

L42 ANSWER 4 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 121524-11-6 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride, [S-(R*,R*)]-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN SR 58613A
FS STEREOSEARCH
MF C22 H26 Cl N O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (135025-88-6)

Absolute stereochemistry.



● HCl

5 REFERENCES IN FILE CA (1962 TO DATE)
5 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 121:230444

REFERENCE 2: 117:185365

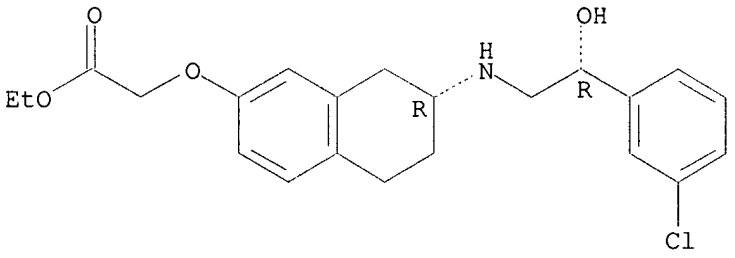
REFERENCE 3: 117:163882

REFERENCE 4: 113:165225

REFERENCE 5: 111:39023

L42 ANSWER 5 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 121524-10-5 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride, [R-(R*,R*)]-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN SR 58612A
FS STEREOSEARCH
MF C22 H26 Cl N O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS, DDFU, DRUGU, USPATFULL
CRN (121524-07-0)

Absolute stereochemistry.



HCl

5 REFERENCES IN FILE CA (1962 TO DATE)
5 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 121:230444

REFERENCE 2: 117:185365

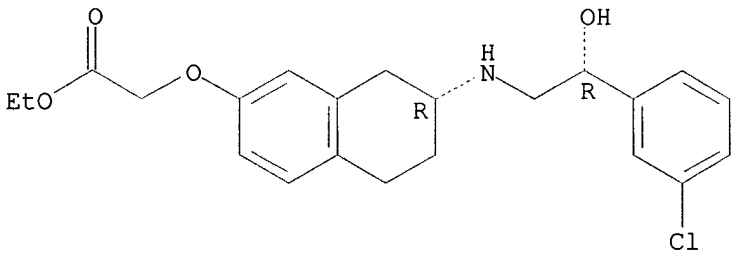
REFERENCE 3: 117:163882

REFERENCE 4: 113:165225

REFERENCE 5: 111:39023

L42 ANSWER 6 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 121524-07-0 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C22 H26 Cl N O4**
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

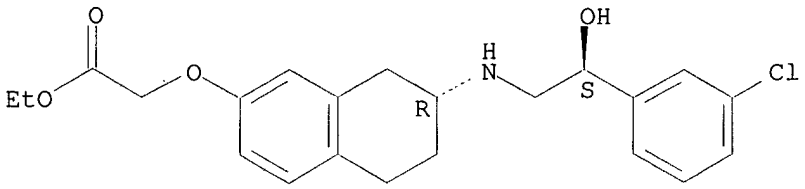
REFERENCE 1: 121:230444

REFERENCE 2: 115:57179

REFERENCE 3: 111:39023

L42 ANSWER 7 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 121489-36-9 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride, (R*,S*)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride, (R*,S*)-(.+-.)-
OTHER NAMES:
CN SR 58538B
FS STEREOSEARCH
MF C22 H26 Cl N O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (121489-32-5)

Relative stereochemistry.



● HCl

2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 111:146279

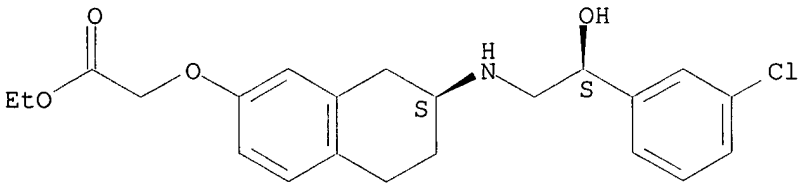
REFERENCE 2: 111:39023

L42 ANSWER 8 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 121489-35-8 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, (R*,R*)-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, (R*,R*)-(.+-.)-, trifluoroacetate (salt)
FS STEREOSEARCH
MF C22 H26 Cl N O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

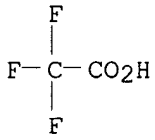
CRN 121489-34-7
CMF C22 H26 Cl N O4

Relative stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

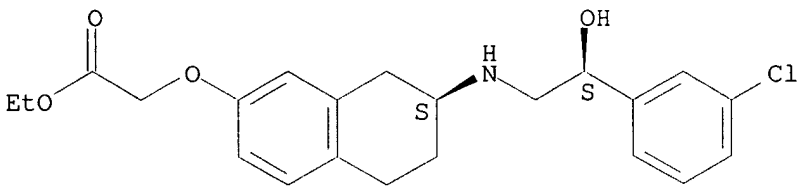


1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 111:39023

L42 ANSWER 9 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 121489-34-7 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, (R*,R*)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, (R*,R*)-(.+-.)-
FS STEREOSEARCH
MF **C22 H26 Cl N O4**
CI COM
SR CA

Relative stereochemistry.



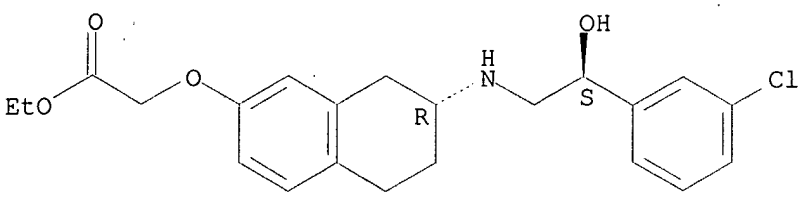
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L42 ANSWER 10 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 121489-33-6 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, (R*,S*)-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, (R*,S*)-(.+-.)-, trifluoroacetate (salt)
FS STEREOSEARCH
MF C22 H26 Cl N O4 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

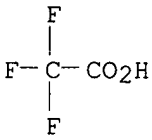
CRN 121489-32-5
CMF C22 H26 Cl N O4

Relative stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

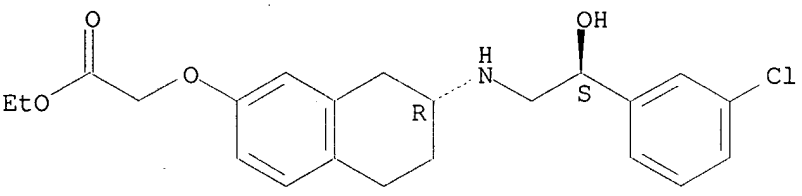


1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 111:39023

L42 ANSWER 11 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 121489-32-5 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, (R*,S*)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, (R*,S*)-(.+-.)-
FS STEREOSEARCH
MF **C22 H26 Cl N O4**
CI COM
SR CA

Relative stereochemistry.

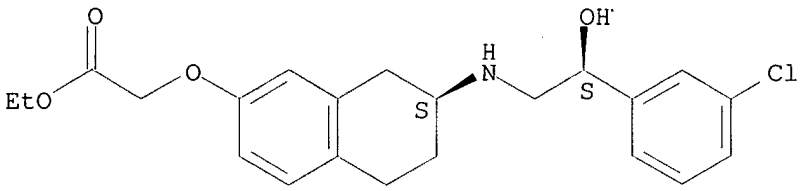


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L42 ANSWER 12 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 120839-54-5 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride, (R*,R*)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride, (R*,R*)-(.+-.)-
OTHER NAMES:
CN SR 58539B
FS STEREOSEARCH
MF C22 H26 Cl N O4 . Cl H
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, EMBASE, USPATFULL
CRN (121489-34-7)

Relative stereochemistry.



● HCl

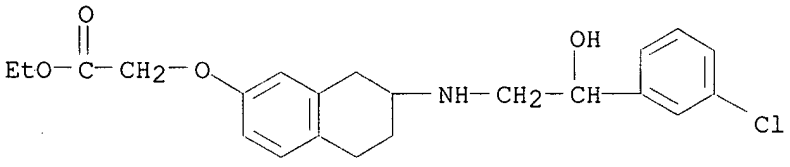
3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 111:146279

REFERENCE 2: 111:39023

REFERENCE 3: 110:225302

L42 ANSWER 13 OF 13 REGISTRY COPYRIGHT 2002 ACS
RN 107758-27-0 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SR 58380
FS 3D CONCORD
MF **C22 H26 Cl N O4**
CI COM
SR CA
LC STN Files: ADISINSIGHT, CA, CAPLUS, CASREACT, SYNTHLINE, USPATFULL



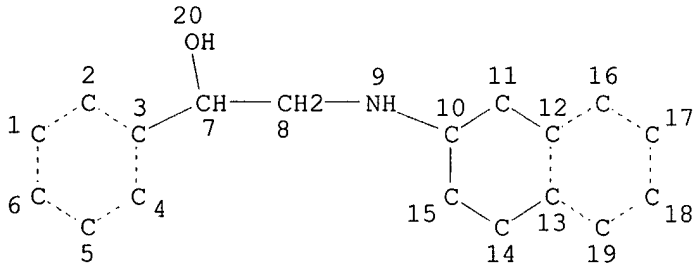
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 120:153732

REFERENCE 2: 106:156084

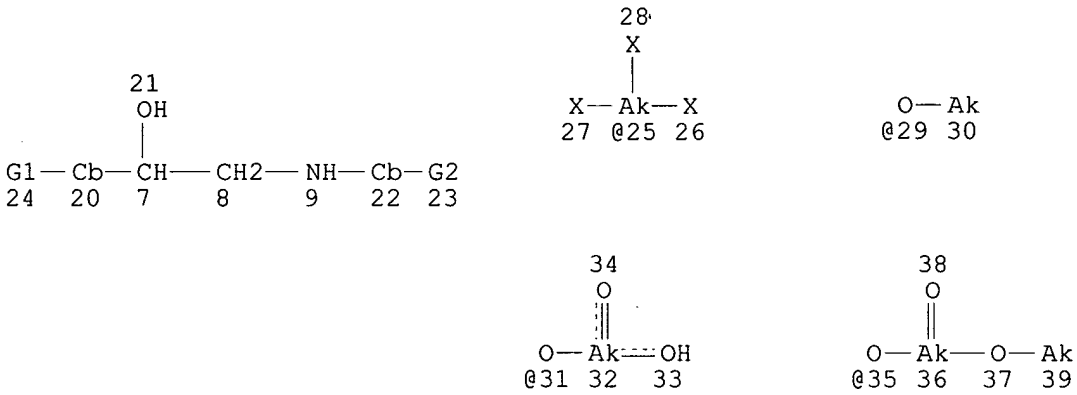
=> d sta que l93
L85 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L87 375 SEA FILE=REGISTRY SSS FUL L85
L88 STR



VAR G1=H/X/AK/25
VAR G2=OH/29/31/35
NODE ATTRIBUTES:
CONNECT IS M1 RC AT 25
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 20
GGCAT IS PCY AT 22
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 23

STEREO ATTRIBUTES: NONE
L90 237 SEA FILE=REGISTRY SUB=L87 SSS FUL L88
L93 76 SEA FILE=REGISTRY SUB=L90 CSS FUL L88

100.0% PROCESSED 237 ITERATIONS 76 ANSWERS

SEARCH TIME: 00.00.01

=> d his l93-

(FILE 'REGISTRY' ENTERED AT 09:45:36 ON 13 OCT 2002)
L93 76 S L88 CSS FUL SUB=L90
SAV L93 JKIM44531D/A
L94 161 S L90 NOT L93
L95 61 S L93 NOT L41,L42

FILE 'HCAPLUS' ENTERED AT 10:12:57 ON 13 OCT 2002
L96 18 S L95
L97 18 S L96 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L98 13 S L97 AND L71
L99 49 S L71,L97,L98

FILE 'REGISTRY' ENTERED AT 10:14:11 ON 13 OCT 2002

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 10:14:26 ON 13 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 13 Oct 2002 VOL 137 ISS 16
FILE LAST UPDATED: 11 Oct 2002 (20021011/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d l99 bib abs hitrn retable tot

L99 ANSWER 1 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:521902 HCAPLUS
DN 135:103720
TI Method of reducing nicotine and tobacco craving in mammals
IN Coffin, Vicki L.; Glue, Paul W.
PA Schering Corp., USA
SO U.S., 20 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI US 6262049 B1 20010717 US 1998-178447 19981023 <--
US 2001025038 A1 20010927 US 2001-846170 20010501 <--
PRAI US 1997-64563P P 19971028 <--
US 1998-178447 A3 19981023
AB A method of reducing cravings in a mammal to nicotine or tobacco is disclosed. The method comprises administering to the mammal an effective amt. of a D1/D5 antagonist or a D1/D5 partial agonist alone or in combination with other specified CNS compds.
IT **121524-09-2, SR 58611a**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(method of reducing nicotine and tobacco craving in mammals)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	1996			WO 9613257	HCAPLUS
Anon	1997			WO 9746239	HCAPLUS
Anon	1999			WO 9915161	HCAPLUS
Bednar	1995	269	R896	American J of Physio	MEDLINE
Caine, S	1994	270	209	The Journal of Pharm	HCAPLUS
Cervo	1996	731	31	Brain Research	HCAPLUS
Cervo, L	1995	673	242	Brain Research	HCAPLUS
Corrigall	1994	48	817	Pharmacology Biochem	HCAPLUS
Dry, W	1993	10	207	Alcohol	
Dyr				Biological Abstracts	
Gordon, Y	1994		365	European Journal of	
Ng	1994			Medline Abstracts, a	
Nielsen	1985	11	167	European Journal of	
Panocka, I	1995	120	227	Psychopharmacology	HCAPLUS
Paul, A	1993	21		JACC	HCAPLUS
Samochowiec	1995	50	815	Pharmazie	HCAPLUS
Sydney, A	1996	6	1139	Bioorganic & Medicin	

L99 ANSWER 2 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:743877 HCAPLUS
DN 130:119495
TI Beta-3 adrenergic receptor agonists cause an increase in gastrointestinal transit time in wild-type mice, but not in mice lacking the beta-3 adrenergic receptor
AU Fletcher, Daniel S.; Candelore, Mari Rios; Grujic, Danica; Lowell, Bradford B.; Luell, Silvi; Susulic, Vedrana S.; Macintyre, D. Euan
CS Department of Pharmacology, Merck and Co., Rahway, NJ, USA
SO Journal of Pharmacology and Experimental Therapeutics (**1998**), 287(2), 720-724
CODEN: JPETAB; ISSN: 0022-3565
PB Lippencott Williams & Wilkins
DT Journal
LA English
AB The effects of beta-3 adrenergic receptor (.beta.3-AR) agonists on gastrointestinal (GI) motility, as reported by stomach retention and intestinal transit of radiolabeled charcoal, were compared in wild-type (WT) mice and in transgenic mice lacking .beta.3-AR (.beta.3-AR[KO]) or having .beta.3-AR in white and brown adipose tissue only (.beta.3-AR[WAT + BAT]). After s.c. administration of 3 mg/kg of the selective, rodent specific .beta.3-AR agonists BRL 35135, CL 316,243 or ICI 198,157, WT mice exhibited a significant decrease in the extent of movement of radiotracer through the stomach and intestines, indicative of decreased GI motility. These compds. also caused an increase in plasma glycerol levels in the WT mice, suggesting that increased lipolysis in adipose tissue had been evoked. None of these compds. had an effect on GI motility or evoked lipolysis in the .beta.3-AR[KO] mice. Treatment of WT mice with **SR 58611A**, a .beta.3-AR agonist that exhibited a relatively lower affinity for rodent .beta.3-AR in vitro, did not affect

GI motility or plasma glycerol levels in WT or .beta.3[KO] mice when administered s.c. at 3 mg/kg. Clonidine, an alpha-2 adrenergic receptor agonist, used as a pos. control in these GI studies, caused a decrease in GI motility in both WT and .beta.3-AR[KO] mice. These results are consistent with a postulated role for .beta.3-AR in regulation of GI motility in the mouse. However, treatment of .beta.3-AR[WAT + BAT] mice with 3 mg/kg BRL 35135 resulted in elevated plasma glycerol levels, as well as increased stomach retention and decreased intestinal transit of radiotracer. These results suggest that this .beta.3-AR agonist may exert its effects on the GI tract indirectly, through an unknown signaling mechanism activated by agonism of .beta.3-AR in adipose tissue.

IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(beta-3 adrenergic receptor agonists cause increase in gastrointestinal transit time in wild-type mice but not in mice lacking beta-3 adrenergic receptor in relation to effect of lipolysis by adipose tissue)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Arch, J	1993	13	663	Med Res Rev	HCAPLUS
Arch, J	1984	309	163	Nature	HCAPLUS
Bensaid, M	1993	318	223	FEBS Lett	HCAPLUS
Berkowitz, D	1995	289	223	Eur J Pharmacol	HCAPLUS
Bond, R	1988	95	723	Br J Pharmacol	HCAPLUS
Candelore, M	1996	137	2638	Endocrinology	HCAPLUS
Chang, F	1995	155	457	Acta Physiol Scand	HCAPLUS
Cohen, M	1995	272	446	J Pharmacol Exp Ther	HCAPLUS
Collins, S	1994	8	518	Mol Endocrinol	HCAPLUS
Croci, T	1991	3	273	J Gastrointest Motil	
Croci, T	1988	20	147	Pharmacol Res Commun	HCAPLUS
de Boer, R	1995	116	1945	Br J Pharmacol	HCAPLUS
De Ponti, F	1995	114	1447	Br J Pharmacol	HCAPLUS
De Ponti, F	1996	69	59	Pharmacol Ther	HCAPLUS
Eliasson, B	1995	38	79	Diabetologia	MEDLINE
Emorine, L	1989	245	1118	Science	HCAPLUS
Evans, B	1996	117	210	Br J Pharmacol	HCAPLUS
Giudice, A	1989	44	1411	Life Sci	HCAPLUS
Granneman, J	1991	40	895	Mol Pharmacol	HCAPLUS
Grujic, D	1997	272	17686	J Biol Chem	HCAPLUS
Howe, R	1992	35	1751	J Med Chem	HCAPLUS
Lafontan, M	1993	34	1057	J Lipid Res	HCAPLUS
Landi, M	1993	53	297	Life Sci	
Lezama, E	1996	308	69	Eur J Pharmacol	HCAPLUS
Manara, L	1996	117	435	Br J Pharmacol	HCAPLUS
Manara, L	1995	9	332	Fund Clin Pharmacol	HCAPLUS
Maugeri, S	1994	17	148	J Vet Pharmacol Ther	HCAPLUS
Miller, M	1961	6	211	J Pharmacol Methods	
Muzzin, P	1991	266	24053	J Biol Chem	HCAPLUS
Nahmias, C	1991	10	3721	EMBO J	HCAPLUS
Puig, M	1996	76	A257	Br J Anesthesia	
Spiegelman, B	1996	87	377	Cell	HCAPLUS
Susulic, V	1995	270	29483	J Biol Chem	HCAPLUS
Thollander, M	1996	8	143	Neurogastroenterol M	MEDLINE
van der Vliet, A	1990	255	218	J Pharmacol Exp Ther	HCAPLUS
Yoshida, T	1996	45	787	Metabolism	HCAPLUS

L99 ANSWER 3 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:557719 HCAPLUS
DN 129:270414
TI Effects of .beta.3-adrenoceptor agonist **SR 58611A** on

gastric acid secretion and histamine release in the dog: comparison with ritodrine
AU Bertini, Simone; Coruzzi, Gabriella; Intorre, Luigi; Soldani, Giulio
CS Laboratory of Pharmacology, Faculty of Veterinary Medicine, University of Pisa, Pisa, I-56124, Italy
SO General Pharmacology (**1998**), 31(4), 625-631
CODEN: GEPHDP; ISSN: 0306-3623
PB Elsevier Science Inc.
DT Journal
LA English
AB The involvement of .beta.3 adrenoceptors in the control of gastric acid secretion and histamine release was investigated in the dog. In conscious dogs, **SR 58611A** (0.0625-1.0 mg/kg/h IV) dose dependently inhibited gastric acid secretion induced by pentagastrin. Maximal inhibition (40%) was obtained with the dose of 1 mg/kg. Ritodrine (1 mg/kg/h IV) also induced a marked inhibition (85%) of gastric acid secretion stimulated by pentagastrin. On 2-deoxy-d-glucose-stimulated acid secretion, both **SR 58611A** and ritodrine at 1 mg/kg/h IV showed inhibitory effects. On these expts., ritodrine, but not **SR 58611A**, significantly reduced plasma gastrin concns. In anesthetized dogs, histamine concns. from gastrosplenic vein increased fivefold after the infusion of pentagastrin. **SR 58611A** (1 mg/kg/h IV) did not significantly modify the stimulant effect of pentagastrin on histamine release. In contrast, ritodrine (1 mg/kg/h IV) significantly inhibited histamine release induced by pentagastrin. These data suggest that .beta.3 adrenoceptors may participate in the neg. control of gastric acid secretion in the dog, probably through a histamine-independent mechanism.
IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.3-adrenoceptor agonist **SR 58611A** effects on gastric acid secretion and histamine release in the dog in comparison with ritodrine)

L99 ANSWER 4 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:306016 HCAPLUS
DN 129:76216
TI Influence of .beta.-adrenoceptor agonists on the pulmonary circulation. Effects of a .beta.3-adrenoceptor antagonist, SR 59230A
AU Dumas, Monique; Dumas, Jean-Paul; Bardou, Marc; Rochette, Luc; Advenier, Charles; Giudicelli, Jean-Francois
CS Laboratoire de Physiopathologie et de Pharmacologie Cardiovasculaires Experimentales, Faculte de Medecine, Dijon, 21000, Fr.
SO European Journal of Pharmacology (**1998**), 348(2/3), 223-228
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB The aims of this study were (a) to compare in the rat isolated perfused lung prepn., the effects of isoprenaline and of three .beta.3-adrenoceptors agonists, SR 59104A, [N-[[6-hydroxy-1,2,3,4-tetrahydronaphthalen-(2R)-2yl]methyl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine-HCl], SR 59119A [N-[[7-methoxy-1,2,3,4-tetrahydronaphtalen-(2R)-2yl]methyl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine-HCl] and **SR 58611A** [ethyl [(7S)-7-[(2R)-2-(3-chlorophenyl)-2-hydroxyethylamino]-5,6,7,8-tetrahydronaphthalen-2-yloxy]acetate-HCl] on hypoxia-induced pulmonary vasoconstriction, and (b) to investigate the potential existence of atypical .beta.-adrenoceptors in these effects. Propranolol (0.1 .mu.M) was used to antagonize .beta.1- and .beta.2-adrenoceptors whereas SR 59230A, 3-(2-ethylphenoxy)-1-[(1S)-1,2,3,4-tetrahydronapht-1-ylamino]-(2S)-2-propanol oxalate) (0.3 .mu.M) was used to block .beta.3-adrenoceptors.

Isoprenaline and the three .beta.3-adrenoceptors agonists caused concn.-dependent relaxations during the pulmonary pressure response. Propranolol and SR 59230A inhibited the relaxant effects of isoprenaline. SR 59230A but not propranolol inhibited those of SR 59104A. Finally, propranolol and SR 59230A failed to oppose SR 59119A- and **SR 58611A**-induced relaxant effects. In concns. .gtoreq.1 .mu.M, SR 59230A caused per se a relaxation of the hypoxic vasoconstricted lung. These results suggest the existence of atypical .beta.-adrenoceptors in the rat pulmonary vessels.

IT **121524-09-2, SR58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-adrenoceptor agonists and .beta.3-adrenoceptor antagonist SR 59230A effect on pulmonary circulation)

L99 ANSWER 5 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:122129 HCAPLUS
DN 128:239539
TI Validity of (-)-[3H]-CGP 12177A as a radioligand for the "putative .beta.4-adrenoceptor" in rat atrium
AU Sarsero, Doreen; Molenaar, Peter; Kaumann, Alberto J.
CS Department of Pharmacology, University of Melbourne, Parkville, 3052, Australia
SO British Journal of Pharmacology (1998), 123(3), 371-380
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton Press
DT Journal
LA English
AB We have recently suggested the existence in the heart of a "putative .beta.4-adrenoceptor" based on the cardiostimulant effects of non-conventional partial agonists, compds. that cause cardiostimulant effects at greater concns. than those required to block .beta.1- and .beta.2-adrenoceptors. We sought to obtain further evidence by establishing and validating a radioligand binding assay for this receptor with (-)-[3H]-CGP 12177A ((-)-4-(3-tertiarybutylamino-2-hydroxypropoxy) benzimidazol-2-one) in rat atrium. We investigated (-)-[3H]-CGP 12177A for this purpose for two reasons, because it is a non-conventional partial agonist and also because it is a hydrophilic radioligand. Increasing concns. of (-)-[3H]-CGP 12177A, in the absence or presence of 20 .mu.M (-)-CGP 12177A to define non-specific binding, resulted in a biphasic satn. isotherm. Low concns. bound to .beta.1- and .beta.2-adrenoceptors (pKD 9.4.+-.0.1, Bmax 26.9.+-.3.1 fmol mg-1 protein) and higher concns. bound to the "putative .beta.4-adrenoceptor" (pKD 7.5.+-.0.1, Bmax 47.7.+-.4.9 fmol mg-1 protein). In other expts. designed to exclude .beta.1- and .beta.2-adrenoceptors, (-)-[3H]-CGP 12177A (1-200 nM) binding in the presence of 500 nM (-)-propranolol was also saturable (pKD 7.6.+-.0.1, Bmax 50.8.+-.7.4 fmol mg-1 protein). The non-conventional partial agonists (-)-CGP 12177A (pKi 7.3.+-.0.2), (.+-.)-cyanopindolol (pKi 7.6.+-.0.2), (-)-pindolol (pKi 6.6.+-.0.1) and (.+-.)-carazolol (pKi 7.2.+-.0.2) and the antagonist (-)-bupranolol (pKi 6.6.+-.0.2), all competed for (-)-[3H]-CGP 12177A binding in the presence of 500 nM (-)-propranolol at the "putative .beta.4-adrenoceptor", with affinities closely similar to potencies and affinities detd. in organ bath studies. The catecholamines competed with (-)-[3H]-CGP 12177A at the "putative .beta.4-adrenoceptor" in a stereoselective manner, (-)-noradrenaline (pKiH 6.3.+-.0.3, pKiL 3.5.+-.0.1), (-)-adrenaline (pKiH 6.5.+-.0.2, pKiL 2.9.+-.0.1), (-)-isoprenaline (pKiH 6.2.+-.0.5, pKiL 3.4.+-.0.1), (+)-isoprenaline (pKi<1.7), (-)-RO363 ((-)-(1-(3,4-dimethoxyphenethylamino)-3-(3,4-dihydroxyphenoxy)-2-propranol)oxalate, pKi 5.5.+-.0.1). The inclusion of guanosine 5-triphosphate (GTP 0.1 mM) had no effect on binding of (-)-CGP 12177A or (-)-isoprenaline to the "putative .beta.4-adrenoceptor". In competition binding studies, (-)-CGP 12177A competed with (-)-[3H]-CGP 12177A for one receptor state in the

absence (pKi 7.3.+-.0.2) or presence of GTP (pKi 7.3.+-.0.2). (-)-Isoprenaline competed with (-)-[3H]-CGP 12177A for two states in the absence (pKiH 6.6.+-.0.3, pKiL 3.5.+-.0.1; % H 25.+-.7) or presence of GTP (pKiH 6.2.+-.0.5, pKiL 3.4.+-.0.1; % H 37.+-.6). In contrast, at .beta.1-adrenoceptors, GTP stabilized the low affinity state of the receptor for (-)-isoprenaline. The specificity of binding to the "putative .beta.4-adrenoceptor" was tested with compds. active at other receptors. High concns. of the .beta.3-adrenoceptor agonists, BRL 37344 ((RR + SS)[4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenoxy]acetic acid, 6 .mu.M), **SR 58611A** (ethyl{(7S)-7-[(2R)-2-(3-chlorophenyl)-2-hydroxyethylamino]-5,6,7,8-tetrahydronaphtyl-2-yloxy}acetate hydrochloride, 6 .mu.M), ZD 2079 ((.+-.)-1-phenyl-2-(2-4-carboxymethylphenoxy)-ethylamino)-ethan-1-ol, 60 .mu.M, CL 316243 (disodium (R,R)-5-[2-[2-(3-chlorophenyl)-2-hydroxyethyl-amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate, 60 .mu.M) and antagonist SR 59230A (3-(2-ethylphenoxy)-1-[(1S)-1,2,3,4-tetrahydronaphth-1-ylamino]-2S-2-propanol oxalate, 6 .mu.M) caused less than 22% inhibition of (-)-[3H]-CGP 12177A binding in the presence of 500 nM (-)-propranolol. Histamine (1 mM), atropine (1 .mu.M), phentolamine (10 .mu.M), 5-HT (100 .mu.M) and the 5-HT4 receptor antagonist SB 207710 ((1-butyl-4-piperidinyl)-Me-8-amino-7-iodo-1,4-benzodioxan-5-carboxylate, 10 nM) caused less than 26% inhibition of binding. Non-conventional partial agonists, the antagonist (-)-bupranolol and catecholamines all competed for (-)-[3H]-CGP 12177A binding in the absence of (-)-propranolol at .beta.1-adrenoceptors, with affinities (pKi) ranging from 1.6-3.6 log orders greater than at the "putative .beta.4-adrenoceptor". We have established and validated a radioligand binding assay in rat atrium for the "putative .beta.4-adrenoceptor" which is distinct from .beta.1-, .beta.2- and .beta.3-adrenoceptors. The stereoselective interaction with the catecholamines provides further support for the classification of the receptor as "putative .beta.4-adrenoceptor".

IT **121524-09-2, SR 58611A**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(validity of (-)-[3H]-CGP 12177A as a radioligand for putative .beta.4-adrenoceptor in rat atrium in relation to competitive binding assays with other agonists and antagonists)

L99 ANSWER 6 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:87713 HCAPLUS
DN 128:154013
TI Preparation of 3-(2-pyridylaminoalkyl)-1-phenoxypropanolamines having .beta.3-adrenergic antagonist activity
IN Badone, Domenico; Cecchi, Roberto; Croci, Tiziano; Guzzi, Umberto; Manara, Luciano
PA Sanofi, Fr.; Badone, Domenico; Cecchi, Roberto; Croci, Tiziano; Guzzi, Umberto; Manara, Luciano
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

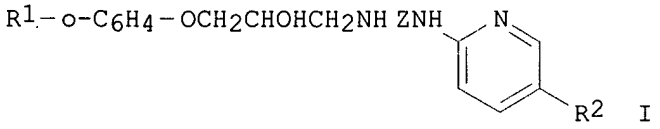
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9803485	A1	19980129	WO 1997-FR1360	19970722 <--

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

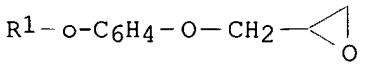
	FR 2751646	A1	19980130	FR 1996-9203	19960723 <--
	FR 2751646	B1	19990122		
	AU 9738529	A1	19980210	AU 1997-38529	19970722 <--
PRAI	FR 1996-9203		19960723 <--		
	WO 1997-FR1360		19970722 <--		

OS CASREACT 128:154013; MARPAT 128:154013

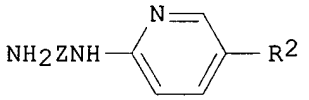
GI



I



II



III

AB 1-(2-Alkylphenoxy)-3-(2-pyridylaminoalkylamino)propan-2-ols I (R1 = C3-C7 alkyl or C3-C7 cycloalkyl; R2 = H, electron-accepting group; Z = C2-C3 alkylene), their salts, enantiomers, and pharmaceutical compns. contg. I having .beta.3-adrenergic receptor antagonist activity are disclosed. as is a method for prepg. them. Compds. I are prepd. via reaction of 1,2-epoxypropanes II with N-(2-pyridyl)alkylenediamines III. Thus, reaction of 3-(2-tert-butylphenoxy)-1,2-epoxypropane (prepn. given) with N-(5-nitro-2-pyridinyl)ethylenediamine in refluxing EtOH overnight afforded 1-(2-tert-butylphenoxy)-3-[2-(5-nitro-2-pyridinylamino)ethylamino]propan-2-ol, which was converted to its hydrochloride salt. Chlorohydrates of racemic I inhibited the thermogenic effect induced by **SR 58611** in an in vivo study of their .beta.3-antagonist activity on brown fat tissue receptors in rat. Pharmaceutically acceptable compns. contg. I are discussed.

L99 ANSWER 7 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:806284 HCAPLUS
DN 128:113275
TI Comparison between .beta.3 and .beta.2 adrenoceptor agonists as inhibitors of gastric acid secretion
AU Coruzzi, G.; Spaggiari, S.; Bertaccini, G.
CS Institute Pharmacology, University Parma, Parma, 43100, Italy
SO Journal of Physiology (Paris) (**1997**), 91(3-5), 241-246
CODEN: JHYSEM; ISSN: 0928-4257
PB Editions Scientifiques et Medicales Elsevier
DT Journal
LA English
AB In order to investigate the role of .beta.3 adrenoceptors in the regulation of gastric acid secretion we studied the effects of compd. **SR58611A** (a selective agonist for atypical .beta. adrenoceptors), alone or in combination with .beta.-adrenoceptor antagonists, in the gastric fistula of a conscious cat. The effects of **SR58611A** were compared with those of clenbuterol, a selective agonist for .beta.2 adrenoceptors. I.v. infusion of **SR58611A** (0.3-3 .mu.mol/kg/h) caused a dose-dependent, but partial, inhibition of the acid secretory response to 2-deoxy-D-glucose 100 mg/kg i.v., max. effect not exceeding 40%. Clenbuterol (0.03-0.1 .mu.mol/kg/h) caused a similar effect (max.

inhibition about 50%) at doses approx. 30 times lower. The acid secretion induced by the histamine H2-receptor agonist dimaprit (1 .mu.mol/kg/h) was minimally affected by both .beta. adrenoceptor agonists. The inhibitory effect of **SR58611A** (3 .mu.mol/kg/h) on 2-deoxy-D-glucose-induced acid secretion was not modified by pretreatment with the non-selective .beta.1- and .beta.2-adrenoceptor blocker propranolol, administered at doses (1.5 .mu.mol/kg i.v.) that completely blocked the inhibitory effect of clenbuterol (0.1 .mu.mol/kg/h). In contrast, bupranolol (10 .mu.mol/kg i.v.)(a drug endowed with .beta.3 antagonistic properties) prevented the inhibitory effects of both **SR58611A** and clenbuterol. The present data provide functional evidence that, besides .beta.2-, also .beta.3-adrenoceptors can have neg. effects on gastric acid secretion, particularly when it is stimulated by indirect stimuli, like 2-deoxy-D-glucose. This gastric antisecretory activity may represent an addnl. mechanism for the physio-pharmacol. control of gastric acid secretion.

IT **121524-09-2, SR58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(comparison between .beta.3 and .beta.2 adrenoceptor agonists as inhibitors of gastric acid secretion)

L99 ANSWER 8 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:751676 HCAPLUS
DN 128:84320
TI Lipolytic effects of conventional .beta.3-adrenoceptor agonists and of CGP 12,177 in rat and human fat cells: preliminary pharmacological evidence for a putative .beta.4-adrenoceptor
AU Galitzky, Jean; Langin, Dominique; Verwaerde, Patrick; Montastruc, Jean-Louis; Lafontan, Max; Berlan, Michel
CS Laboratoire de Pharmacologie Medicale et Clinique, Unite 317 Institut National de la Sante et de la Recherche Medicale, Faculte de Medecine, Universite Paul Sabatier, Toulouse, 31073, Fr.
SO British Journal of Pharmacology (**1997**), 122(6), 1244-1250
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton Press
DT Journal
LA English
AB The nature of rat and human fat cell .beta.3-adrenoceptors was investigated by studying the effects of the new .beta.3-adrenoceptor selective antagonist, SR 59,230A, on lipolysis induced by the conventional .beta.3-adrenoceptor agonists, CL 316,243 and **SR 58, 611A**, and by the non-conventional partial .beta.3-adrenoceptor agonist CGP 12,177 (a potent .beta.1- and .beta.2-adrenoceptor antagonist with partial .beta.3-adrenoceptor agonist property). In rat fat cells, the rank order of potency of agonists was: CL 316,243 > isoprenaline > **SR 58,611A** > CGP 12,177. The three former agents were full agonists whereas CGP 12,177 was a partial agonist (intrinsic activity of 0.70). In human fat cells, the lipolytic effect of CGP 12,177 reached 25 % of isoprenaline effect. CL 316,243 was a poor inducer of lipolysis and **SR 58,611A** was ineffective. In rat fat cells, lipolysis induced by CL 316,243 and **SR 58,611A** was competitively antagonized by SR 59,230A. Schild plots were linear with pA2 values of 6.89 and 6.37, resp. Conversely, 0.1, 0.5 and 1 .mu.M SR 59,230A did not modify the concn.-response curve of CGP 12,177. A rightward shift of the curve was however obsd. with 10 and 100 .mu.M of SR 59,230A. The apparent pA2 value was 5.65. The non-selective .beta.-adrenergic antagonist, bupranolol, competitively displaced the concn.-response curve of CGP 12,177 and CL 316,243. Schild plots were linear with pA2 values of 6.70 and 7.59, resp. CL316,243-mediated lipolytic effect was not antagonized by CGP 20,712A. In human fat cells, CGP 12,177-mediated lipolytic effect was antagonized by bupranolol and CGP 20,712A. SR 59,230A (0.1, 1 and 10 .mu.M) did not

modify the concn.-response curve of CGP 12,177. A rightward shift was however obsd. at 100 .mu.M leading to an apparent pA2 value of 4.32. The results suggest that the non-conventional partial agonist CGP 12,177 can activate lipolysis in fat cells through the interaction with a .beta.-adrenoceptor pharmacol. distinct from the .beta.3-adrenoceptor, i.e. through a putative .beta.4-adrenoceptor. They suggest that the two subtypes coexist in rat fat cells whereas only the putative .beta.4-adrenoceptor mediates lipolytic effect of CGP 12,177 in human fat cells.

IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(lipolytic effects of conventional .beta.3-adrenoceptor agonists and of CGP 12,177 in rat and human fat cells and evidence for a putative .beta.4-adrenoceptor)

L99 ANSWER 9 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:567066 HCAPLUS
DN 127:275950
TI Characterization of a novel iodocyanopindolol and SM-11044 binding protein, which may mediate relaxation of depolarized rat colon tonus
AU Sugasawa, Toshinari; Matsuzaki-Fujita, Masago; Guillaume, Jean-Luc; Camoin, Luc; Morooka, Shigeaki; Strosberg, A. Donny
CS Institut Cochin de Genetique Moleculaire, CNRS-UPR 0415 and Universite Paris VII, Paris, 75014, Fr.
SO Journal of Biological Chemistry (1997), 272(34), 21244-21252
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Studies under blockade of .alpha.-, .beta.1-, and .beta.2-adrenoreceptors revealed a good correlation between the responses of rat colon relaxation of depolarized tonus and of rat adipocyte lipolysis elicited by catecholamines or BRL-37344, a selective .beta.3-adrenoreceptor agonist, suggesting .beta.3-adrenoreceptor stimulation. In contrast, SM-11044, a nonselective .beta.-adrenoreceptor agonist, stimulated colon relaxation more efficiently than lipolysis; its effects were differently antagonized by cyanopindolol with pA2 values of 8.31 in colon and of 7.32 in adipocytes. Binding studies in rat colon smooth muscle membranes using [125I]iodocyanopindolol under blockade of adrenaline and serotonin receptors revealed the existence of a single class of sites (Kd = 11.0 nM, Bmax = 716.7 fmol/mg protein). The specific binding was saturable and reversible and was displaced by SM-11044 but not by BRL-37344, isoproterenol, noradrenaline, adrenaline, serotonin, nor dopamine. This binding site was photoaffinity labeled using [125I]iodocyanopindolol-diazirine. The labeling was prevented by SM-11044 but not by BRL-37344. The amino-terminal amino acid sequences of the high performance liq. chromatog.-purified peptides generated by enzymic and chem. cleavages of the affinity labeled 34-kDa protein confirmed that the novel iodocyanopindolol or SM-11044 binding protein of rat colon smooth muscle membranes is different from known adrenaline, serotonin, or dopamine receptors. Its functional role might include the relaxation of depolarized colon.

IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(adrenoreceptor agonist effects on colon smooth muscle relaxation and white adipocyte lipolysis and characterization of iodocyanopindolol-binding protein which mediates adrenoreceptor-independent relaxation in colon smooth muscle)

L99 ANSWER 10 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:475527 HCAPLUS

DN 127:214919
TI The .beta.3-adrenoceptor agonist **SR58611A** inhibits gastric acid secretion in the conscious cat
AU Coruzzi, Gabriella; Bertaccini, G.
CS Institute of Pharmacology, University of Parma, Parma, I-43100, Italy
SO Naunyn-Schmiedeberg's Archives of Pharmacology (**1997**), 356(2), 263-265
CODEN: NSAPCC; ISSN: 0028-1298
PB Springer
DT Journal
LA English
AB The effect of the .beta.3-adrenoceptor agonist [N-((2S)-7-ethoxycarbonylmethoxyl-1,2,3,4-tetrahydronaphth-2-yl) (2R)-2-(3-chlorophenyl)-2-hydroxyethanamine hydrochloride] (**SR58611A**) on gastric acid secretion was investigated in conscious cats with a gastric fistula. The i.v. infusion of **SR58611A** (0.3-3 .mu.mol/kg/h) caused a dose-dependent inhibition of the acid secretion stimulated by 2-deoxy-D-glucose (2DG), with a max. redn. by 45%. The secretory effect of the histamine H2-receptor agonist dimaprit only tended to be reduced by **SR58611A** (3 .mu.mol/kg/h). The inhibitory effect of **SR58611A** was not modified by the non selective .beta.1- and .beta.2-adrenoceptor antagonist propranolol (1.5 .mu.mol/kg i.v.), but it was prevented by bupranolol (10 .mu.mol/kg i.v.), a drug endowed with .beta.3-antagonistic properties. Both antagonists blocked the inhibitory effect of the .beta.2-adrenoceptor agonist clenbuterol (0.1.mu.mol/kg/h) on 2DG-induced acid secretion. These findings suggest that compd. **SR58611A** inhibits gastric acid secretion in the conscious cat through activation of .beta.3-adrenoceptors insensitive to propranolol.
IT **121524-09-2, SR58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(.beta.3-adrenoceptor agonist **SR58611A** inhibition of gastric acid secretion in conscious cat, and comparison with .beta.2-adrenoceptor agonist clenbuterol)

L99 ANSWER 11 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:433633 HCAPLUS
DN 127:55894
TI Stable freeze-dried pharmaceutical formulation containing mannitol and alanine
IN Bouloumie, Colette; Breul, Thierry; Colliere, Laurence; Faure, Philippe
PA Sanofi, Fr.; Bouloumie, Colette; Breul, Thierry; Colliere, Laurence; Faure, Philippe
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9717064	A1	19970515	WO 1996-FR1706	19961030 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2740686	A1	19970509	FR 1995-13022	19951103 <--
FR 2740686	B1	19980116		
CA 2234140	AA	19970515	CA 1996-2234140	19961030 <--

AU 9674990	A1	19970529	AU 1996-74990	19961030 <--
AU 713383	B2	19991202		
EP 858325	A1	19980819	EP 1996-937367	19961030 <--
EP 858325	B1	20020731		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CN 1203527	A	19981230	CN 1996-198786	19961030 <--
BR 9611367	A	19990223	BR 1996-11367	19961030 <--
JP 11507945	T2	19990713	JP 1996-517912	19961030 <--
CZ 287178	B6	20001011	CZ 1998-1231	19961030 <--
IL 124214	A1	20010128	IL 1996-124214	19961030 <--
RU 2163801	C2	20010310	RU 1998-110638	19961030 <--
AT 221374	E	20020815	AT 1996-937367	19961030 <--
ZA 9609176	A	19980430	ZA 1996-9176	19961031 <--
TW 442295	B	20010623	TW 1996-85114410	19961122 <--
NO 9801967	A	19980630	NO 1998-1967	19980430 <--
US 6284277	B1	20010904	US 1998-66387	19981209 <--
PRAI FR 1995-13022	A	19951103 <--		
WO 1996-FR1706	W	19961030 <--		

AB A pharmaceutically acceptable freeze-dried formulation consisting of an amorphous phase and a cryst. phase and including at least one non-protein active principle is disclosed. The formulation is characterized in that it contains mannitol and alanine in a ratio R of 0.1-1, where R is the wt. of mannitol over the wt. of alanine. A free-dried pharmaceutical contained SR 57746A 0.44, alanine 72.0, mannitol 36.0, citric acid 30.8, and Polysorbate-80 4.0 mg.

IT **121524-08-1**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(stable freeze-dried pharmaceutical formulation contg. mannitol and alanine)

L99 ANSWER 12 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:349486 HCAPLUS
DN 127:61038
TI Carboxyl-promoted enhancement of selectivity for the .beta.3 adrenergic receptor. Selectivity is enhanced at the level of receptor binding
AU Sher, Philip M.; Fisher, Liesl G.; Skwish, Stephen; Michel, Inge M.; Seiler, Steven M.; Washburn, William N.; Dickinson, Kenneth E. J.
CS Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA
SO Medicinal Chemistry Research (**1997**), 7(2), 109-115
CODEN: MCREEB; ISSN: 1054-2523
PB Birkhaeuser
DT Journal
LA English
AB Four carboxyl-contg., selective .beta.3 adrenergic agonists and their ester or amide derivs. were evaluated for their ability to bind to human .beta.1, .beta.2, and .beta.3 adrenergic receptors. Stimulatory effects on the .beta.3 adrenergic receptor were also measured. The authors conclude that carboxyl-derived .beta.3 functional selectivity likely results, at least in part, from the effect of the carboxyl on binding selectivity.
IT **121524-09-2, SR 58611A 191533-25-2,**
SR 58878
RL: **BAC (Biological activity or effector, except adverse)**; BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(carboxyl-promoted enhancement of selectivity for .beta.3 adrenergic receptor)

L99 ANSWER 13 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:93789 HCAPLUS
DN 126:99317

TI Use of beta3-adrenergic agonists for inducing the release of glucagon-like-peptide
IN Bouloux, Cyril Jacques; Manara, Luciano; Bloom, Stephen Robert
PA Sanofi, Fr.
SO Fr. Demande, 9 pp.
CODEN: FRXXBL
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	FR 2732894	A1	19961018	FR 1995-4448	19950413 <--
	FR 2732894	B1	19970704		
	FR 2734482	A1	19961129	FR 1995-12694	19951027 <--
	FR 2734482	B1	19970814		
	BE 1009698	A3	19970701	BE 1996-294	19960409 <--
	IT 1298492	B1	20000110	IT 1996-TO284	19960412 <--
PRAI	FR 1995-4448	A	19950413 <--		
	FR 1995-12694	A	19951027 <--		

AB Beta3-adrenergic agonists are useful for inducing the release of glucagon-like-peptide. These agonists are administered at 0.01-30 mg/kg body wt. in different dosage forms (no data).
IT **107758-23-6 107758-43-0 121524-08-1**
160696-89-9 185953-96-2
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(beta3-adrenergic agonists for inducing release of glucagon-like-peptide)

L99 ANSWER 14 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:758896 HCAPLUS
DN 126:18641
TI Preparation of novel aryloxypropanolamino(phenyl)propanol compounds as intestinal motility modulating agents
IN Ohno, Norio; Hiratsuka, Kozo; Takenawa, Noriko
PA Tokyo Tanabe Company Limited, Japan
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9632369	A1	19961017	WO 1996-JP1024	19960412 <--
	W: AU, CA, JP, KR, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9652894	A1	19961030	AU 1996-52894	19960412 <--
PRAI	JP 1995-89706		19950414 <--		
	WO 1996-JP1024		19960412 <--		

OS MARPAT 126:18641
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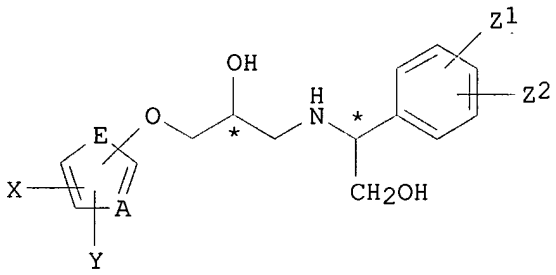

I

AB The title compds. [I; A = CH, N; E = CH:CH, S; X, Y = H, halo, C1-4 alkoxy (un)substituted C1-4 alkoxy, C1-4 alkyl or alkenyl; or X and Y combine to form CH:CH2CH:CH, NHCH:CH; Z1, Z2 = H, halo, (un)substituted C1-4 alkoxy] and salts thereof are prepd. I are useful as active ingredients for controlling intestinal movements. Thus, Et (S)-4-(2-amino-3-hydroxy)propylphenoxyacetate hydrochloride (prepn. given) was refluxed with (2S)-glycidyl Ph ether in 1N caustic soda-EtOH to give 59% Et (S,S)-4-[2-[(3-phenoxy-2-hydroxy)propyl]amino-3-hydroxy]propylphenoxyacetate (II). II in vitro showed EC50 of 28 nM for suppressing rat intestinal movements vs. 14 nM of ref. compd. **SR58611A.**

IT **121524-09-2P, SR58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); PNU (Preparation, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of novel aryloxypropanolamino(phenyl)propanol compds. as intestinal motility modulating agents)

L99 ANSWER 15 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:530176 HCAPLUS
DN 125:186459
TI Differences between the third cardiac .beta.-adrenoceptor and the colonic .beta.3-adrenoceptor in the rat
AU Kaumann, Alberto J.; Molenaar, Peter
CS Dep. Pharmacol., Univ. Melbourne, Victoria, 3052, Australia
SO British Journal of Pharmacology (**1996**), 118(8), 2085-2098
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB The heart of several species including man contains atypical .beta.-adrenoceptors, in addn. to coexisting .beta.1- and .beta.2-adrenoceptors. We now asked the question whether or not the third cardiac .beta.-adrenoceptor is identical to the putative .beta.3-adrenoceptor. We compared the properties of the third cardiac .beta.-adrenoceptor with those of .beta.3-adrenoceptors in isolated tissues of the rat. To study the third cardiac .beta.-adrenoceptor we used spontaneously beating right atria, paced left atria and paced left ventricular papillary muscles. As a likely model for putative .beta.3-adrenoceptors we studied atypical .beta.-adrenoceptors of the colonic longitudinal muscle precontracted with 30 mM KCl. We used .beta.3-adrenoceptor-selective agonists, antagonists and non-conventional partial agonists (i.e., high-affinity blockers of both .beta.1- and B2-adrenoceptors known to exert also stimulant effects through .beta.3-adrenoceptors). The non-conventional partial agonist (-)-CGP 12177 caused pos. chronotropic effects in right atria (pD2 = 7.3) and pos. inotropic effects in left atria (pD2 = 7.5). The stimulant effects of (-)-CGP 12177 were resistant to blockade by 200 nM-2 .mu.M (-)-propranolol

and 3 .mu.M ICI 118551 (a .beta.2-selective antagonist) but antagonized by 1 .mu.M (-)-bupranolol (pKB = 6.4-6.8), 3 .mu.M CGP 20712A (a .beta.1-selective antagonist) (pKB = 6.3-6.4) and 6.6 .mu.M SR 59230A (a .beta.3-selective antagonist, pKB = 5.1-5.4). The non-conventional partial agonist cyanopindolol caused pos. chronotropic effects in right atria (pK2 = 7,7) and pos. inotropic effects in left atria (pD2 = 7.1). The stimulant effects of cyanopindolol were resistant to blockade by 200 nM (-)-propranolol but antagonized by 1 .mu.M (-)-bupranolol (pKB = 6.8-7.1). Neither (-)-CGP 12177 nor cyanopindolol caused stimulant effects in papillary muscles at concns. between 0.2 nM and 20 .mu.M. In the presence of 200 nM (-)-propranolol, the .beta.3-adrenoceptor-selective agonists BRL 37344 (6 .mu.M), **SR 58611A** (6 .mu.M), ZD 2079 (60 .mu.M) and CL 31643 (60 .mu.M) did not cause stimulant effects or modify the potency and efficacy of the effects of (-)-CGP 12177 in right and left atria. The combination of 2 .mu.M (-)-propranolol and 2 .mu.M (-)-noradrenaline did not modify the chronotropic potency and efficacy of (-)-CGP 12177 compared to the potency and efficacy in the presence of 2 .mu.M (-)-propranolol alone. (-)-CGP 12177 relaxed the colon with a pD2 of 6.9 and max. effect of 55% compared to (-)-isoprenaline. The relaxant effects of (-)-CGP 12177 were resistant to blockade by 200 nM (-)-propranolol, 3 .mu.M CGP 20712A, 3 .mu.M ICI 118551 but blocked by 2 .mu.M (-)-propranolol (pKB = 6.0), 1 .mu.M (-)-bupranolol (pKB = 6.4) and 3 .mu.m SR 59230A (pKB = 6.3). In the presence of 200 nM (-)-propranolol, (-)-CGP 12177 (20 .mu.M) antagonized surmountably the relaxant effects of BRL 37344 (pKp = 7.3), (-)-noradrenaline (pKp = 7.0), and CL 316243 (pKp = 7.0). Cyanopindolol in the presence of 200 nM (-)-propranolol relaxed the colon with a pD2 of 7.0 and a max. effect of 40% compared to (-)-isoprenaline. As expected from a partial agonist, cyanopindolol antagonized the relaxant effects of both BRL 37344 and CL 316243 with a pKp = 7.6 and (-)-noradrenaline with a pKp = 7.4. The following .beta.3-adrenoceptor-selective agonists were potent colonic relaxants (pD2 values between parentheses): BRL 37344 (9.1), ZD 2079 (7.0), CL 316243 (9.0) and **SR 58611A** (8.2). The relaxant effects of these agonists were only marginally affected by 200 nM (-)-propranolol, not blocked by 3 .mu.M CGP 20712A or 3 .mu.M ICI 118551, and blocked by SR 59230A 3 .mu.M (pKB = 6.9-7.5), 1 .mu.M (-)-bupranolol (pKB = 6.2-6.4) and 2 .mu.M (-)-propranolol (pKB = 6.3-6.5). The colonic relaxation caused by the nanomolar concns. of the .beta.3-adrenoceptor-selective agonists and the non-conventional partial agonists (-)-CGP 12177 and cyanopindolol and their relative resistance to blockade by antagonists with high affinity for .beta.1- and .beta.2-adrenoceptors but blockade by the .beta.3-adrenoceptor selective SR 59230A agree with the hypothesis that the receptors involved are .beta.3-adrenoceptors. The failure of micromolar concns. of .beta.3-adrenoceptor-selective agonists to produce cardiac stimulation or affect the cardiostimulant effects of (-)-CGP 12177 is inconsistent with the hypothesis that the third cardiac .beta.-adrenoceptor is .beta.3. Addnl., the selective blockade of the colonic putative .beta.3-adrenoceptor compared to the third cardiac .beta.-adrenoceptor by SR 59230A, as well as the blockade of cardiac but not colonic receptors by CGP 20712A is also inconsistent with an identical putative .beta.3-adrenoceptor in colon and heart. We conclude that in the rat the third cardiac .beta.-adrenoceptor is different from the colonic .beta.3-adrenoceptor.

IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. characterization indicates that rat third cardiac .beta.-adrenoceptor is different than colonic .beta.3-adrenoceptor)

L99 ANSWER 16 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:454656 HCAPLUS
DN 125:133456
TI Functional .beta.3-adrenoceptor in the human heart

AU Gauthier, Chantal; Tavernier, Genevieve; Charpentier, Flavien; Langin, Dominique; Le Marec, Herve
CS Fac. Sci. Techniques, Univ. Nantes, Nantes, 44035, Fr.
SO Journal of Clinical Investigation (**1996**), 98(2), 556-562
CODEN: JCINAO; ISSN: 0021-9738
PB Rockefeller University Press
DT Journal
LA English
AB .beta.3-Adrenoceptors are involved in metab., gut relaxation, and vascular vasodilation. However, their existence and role in the human heart have not been documented. We investigated the effects of several .beta.-adrenoceptor agonists and antagonists on the mech. properties of ventricular endomyocardial biopsies. In the presence of nadolol, a .beta.1 and .beta.2-adrenoceptor antagonist, isoprenaline produced consistent neg. inotropic effects. Similar neg. inotropic effects also resulted from the action of .beta.3-adrenoceptor agonists with an order of potency: BRL 37344 > **SR 58611** .apprxeq. CL 316243 > CGP 12177. The dose-response curve to BRL 37344-decreasing myocardial contractility was not modified by pretreatment with nadolol, but was shifted to the right by bupranolol, a nonselective .beta.-adrenoceptor antagonist. .beta.3-Adrenoceptor agonists also induced a redn. in the amplitude and an acceleration in the repolarization phase of the human action potential. .beta.3-Adrenoceptor transcripts were detected in human ventricle by a polymerase chain reaction assay. These results indicate that: (a) .beta.3-adrenoceptors are present and functional in the human heart; and (b) these receptors are responsible for the unexpected neg. inotropic effects of catecholamines and may be involved in pathophysiol. mechanisms leading to heart failure.
IT **121524-08-1, SR 58611**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.3-adrenoceptor agonist neg. inotropic activity in human heart)

L99 ANSWER 17 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:343723 HCAPLUS
DN 125:75996
TI Effects of several putative .beta.3-adrenoceptor agonists on lipolysis in human omental adipocytes
AU Hoffstedt, J.; Loennqvist, F.; Shimizu, M.; Blaak, E.; Arner, P.
CS Department of Medicine, Huddinge University Hospital, Huddinge, S-14186, Swed.
SO International Journal of Obesity (**1996**), 20(5), 428-434
CODEN: IJOBDP; ISSN: 0307-0565
PB Stockton
DT Journal
LA English
AB Atypical .beta.3-adrenoceptor agonists have attained an increasing interest as potential drugs against obesity and diabetes. However, their pharmacol. actions on the native, human .beta.3-adrenoceptor are not well defined. In the present study, the lipolytic effects of several putative .beta.3-adrenoceptor agonists were investigated in human omental adipocytes. CL 316 243 and CGP 12177 had selective partial .beta.3-agonist effects (pD2 about 4 and 8, resp.); the latter drug is a .beta.1-/.beta.2-adrenoceptor blocker in addn. to its .beta.3-adrenoceptor agonist activity. BRL 37344 and SM 11044 were also partial agonists, but with significant .beta.1 - and/or .beta.2-adrenoceptor agonist properties. Bucindolol, ZD 2079, ICI D7114 and **SR 58611A** were ineffective as lipolytic drugs. In addn., ICI D7114 was a non-selective .beta.1-/.beta.2-/.beta.3-adrenoceptor antagonist in human adipocytes. None of the .beta.3-adrenoceptor agonists tested is an ideal drug for therapeutic use in man (i.e. regarded as a selective and full agonist with high receptor potency). Only CL 316 243 may have a potential therapeutic role, although the potency is very low. CGP 12177 is useful as a ref.

substance for human in vitro studies.

IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(putative .beta.3-adrenoceptor agonists effect on lipolysis in human omental adipocytes in relation to obesity treatment)

L99 ANSWER 18 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:94531 HCAPLUS
DN 124:219871
TI Functional identification of rat atypical .beta.-adrenoceptors by the first .beta.3-selective antagonists, aryloxypropanolaminotetralins
AU Manara, Luciano; Badone, Domenico; Baroni, Marco; Boccardi, Giovanni; Cecchi, Roberto; Croci, Tiziano; Giudice, Antonina; Guzzi, Umberto; Landi, Marco; et al.
CS Research Centre Sanofi Midy, Milan, 20137, Italy
SO British Journal of Pharmacology (**1996**), 117(3), 435-42
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB We have assessed the relative abilities of compds. belonging to the new aryloxypropanolaminotetralin (APAT) class and of the ref. .beta.-adrenoceptor-blocking agent, alprenolol, to antagonize functional responses in vitro and in vivo involving atypical (.beta.3) or conventional (.beta.1 and .beta.2) .beta.-adrenoceptors. The range of pA2 values for three representative APATs against inhibition of spontaneous motility in the rat isolated colon by the selective .beta.3-adrenoceptor agonist, **SR 58611A** (8.1-8.8), was well above similarly calcd. values for non-competitive antagonism of guinea-pig trachea relaxation by salbutamol (.beta.2, 6.5-6.9) and the atrial chronotropic response by isoprenaline (.beta.1, 6.7-7.3). Alprenolol, however, was substantially more potent in antagonizing atrial (pA2, 8.2) and tracheal (pA2, 8.9) responses than **SR 58611A** mediated inhibition of colonic motility (pA2, 6.8). Several APAT isomers with different configurations at the chiral carbons, when tested on isolated organs, presented stringent stereochem. requirements for .beta.3-selectivity, including high antagonist potency-ratios between active and inactive enantiomers. In vivo, the inhibition of colonic motility and the thermogenic response of brown adipose tissue elicited in rats by the selective .beta.3-adrenoceptor agonists **SR 58611A** and BRL 37344 resp. were substantially diminished by the representative APAT, SR 59230A, at oral doses (.ltoreq.5 mg kg-1) well below those half maximally effective (ID50) for preventing .beta.1-(isoprenaline tachycardia .gtoreq.80 mg kg-1) or .beta.2-(salbutamol bronchodilatation, 44 mg kg-1) mediated responses. Alprenolol, as expected, was a less potent and nonselective antagonist of the putative .beta.3-responses. These findings support APATs as the first potent, orally effective selective antagonists at .beta.3-adrenoceptors, and provide final unambiguous evidence that .beta.3-adrenoceptors underlie inhibition of colonic motility and brown adipose tissue thermogenesis in rats.

L99 ANSWER 19 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:76125 HCAPLUS
DN 124:220194
TI Functional studies of the first selective .beta.3-adrenergic receptor antagonist SR 59230A in rat brown adipocytes
AU Nisoli, Enzo; Tonello, Cristina; Landi, Marco; Carruba, Michele O.
CS Sch. Med., Milan Univ., Milan, 20129, Italy
SO Molecular Pharmacology (**1996**), 49(1), 7-14
CODEN: MOPMA3; ISSN: 0026-895X

PB Williams & Wilkins
DT Journal
LA English
AB The SS-enantiomer 3-(2-ethylphenoxy)-1-[(1S)-1,2,3,4-tetrahydronaphth-1-ylaminol]-(2S)-2-propanol oxalate (SR 59230A) is proposed to be the first .beta.3-adrenergic receptor antagonist. The present work shows that SR 59230A, unlike its inactive RR-enantiomer (SR 59483), antagonized a typical B3-adrenergic response in vitro, i.e., **SR 58611A**, the ethyl-[(7s)-7-[[(2R)-2-(3-chlorophenyl)-2-hydroxethyl]amino]-5,6,7,8-tetrahydronaphth-2-yl]oxyacetate hydrochloride- or (-)-4-(3-t-butylamino-2-hydroxypropoxy)benzimidazol-2-one (CGP 12177)-stimulated synthesis of cAMP in rat brown adipose tissue membranes, with pKB values of 8.87 and 8.20. In addn., SR 59230A had no antagonistic effect on forskolin-induced cAMP accumulation in rat interscapular brown adipose tissue. SR 59230A, in contrast to the selective .beta.1- and .beta.2-adrenoceptor antagonists (.+-.)[2-(3-carbamoyl-4-hydroxyphenoxy)-ethylamino]-3-[4(1-methyl-4-trifluoromethyl-2-imidazolyl)-phenoxy]-2 propanol and erythro-(.+-.)-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol-hydrochloride did not counteract the cAMP prodn. induced by (-)-isoprenaline or norepinephrine (NE) in rat brain areas rich in .beta.1- or .beta.2-adrenoceptors, such as frontal cortex and cerebellum. Moreover, in proliferating brown fat cells, in which the .beta.1-adrenoceptor is the only .beta.-adrenergic subtype coupled to cAMP prodn., SR 592301A did not modify the prodn. of cAMP induced by NE, whereas CGP 12177 did. In confluent brown fat cells, in which the .beta.3-adrenoceptor is the functional .beta.-adrenergic subtype coupled to adenylyl cyclase, SR 592301A antagonized the NE-induced cAMP accumulation and glycerol release without affecting their basal values, whereas CGP 12177, which per se stimulated cAMP accumulation and glycerol release, did not change the NE-induced increase of either parameter. Finally, SR 59230A concn.-dependently counteracted the NE-stimulated synthesis of uncoupling protein gene in confluent brown fat cells, which is considered mainly a result of selective stimulation of .beta.3-adrenoceptors. These results provide evidence that the new selective .beta.3-adrenoceptor antagonist can contribute considerably to functional characterization of the .beta.3-adrenoceptors.

L99 ANSWER 20 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:905893 HCAPLUS
DN 124:45714
TI Prophylactics or therapeutics containing .beta.3-adrenergic agonists for pancreatitis, circulation disorders, or diabetic complications
IN Yoshino, Takako; Yamaguchi, Isamu; Kodama, Hiroshi
PA Fujisawa Pharmaceutical Co, Japan
SO Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 07228543	A2	19950829	JP 1994-19431	19940216 <--

OS MARPAT 124:45714
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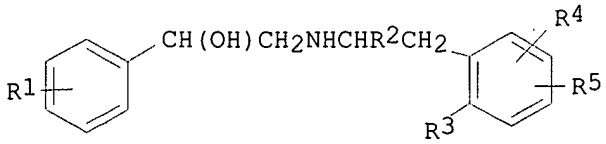

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AB The prophylactic and/or therapeutic agents for pancreatitis, disorders caused from disturbance of circulation, or diabetic complications contain .beta.3-adrenergic agonists as active ingredients. The .beta.3-adrenergic agonists may be bis(phenethyl)amines I (R1 = halo; R2 = lower alkyl and R3 = H or R2R3 = lower alkylene; R4 = lower alkoxy substituted with carboxy which may be esterified and R5 = H or R4R5 = lower alkylenedioxy substituted with carboxy which may be esterified) or their pharmaceutically acceptable salts. (R*,R*)-(.+-.)-[4-[2-[2-(3-chlorophenyl)-2-hydroxyethylamino]propyl]phenoxy]acetic acid Me ester hydrobromide (II) dose-dependently reduced mortality of mice with acute pancreatitis induced by feeding with CDE (choline-deficient ethionine-added) diet at ED50 value 1.0 mg/kg. Capsules contg. II were also formulated.

IT **121524-09-2**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prophylactic and therapeutic agents contg. .beta.3-adrenergic agonists for pancreatitis, circulation disorders, and diabetic complications)

L99 ANSWER 21 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:821445 HCAPLUS
DN 123:247372
TI Differential relevance of .beta.-adrenoceptor subtypes in modulating the rat brown adipocytes function
AU Nisoli, E.; Tonello, C.; Carruba, M. O.
CS School of Medicine, University Milan, Milan, I-20129, Italy
SO Archives Internationales de Pharmacodynamie et de Therapie (**1995**), 329(3), 436-53
CODEN: AIPTAK; ISSN: 0003-9780
PB Heymans Institute of Pharmacology
DT Journal
LA English
AB The potencies and intrinsic activities on cAMP accumulation and lipolysis of various selective .beta.3-adrenoceptor agonists were studied in brown adipocytes and compared to those of the nonselective, (-)-isoprenaline, and conventional .beta.1- (dobutamine) and .beta.2-adrenoceptor (salbutamol) agonists. (-)-Isoprenaline, dobutamine and salbutamol were more potent stimulants of lipolysis than of cAMP accumulation, while the selective .beta.3-adrenoceptor agonists had similar potencies for these two functions. Apparent pA2 values of the selective .beta.1- (CGP 20712A) and .beta.2-adrenoceptor (ICI 118551) antagonists for inhibition of adenylyl cyclase stimulation by (-)-isoprenaline and the .beta.3-adrenoceptor agonists, BRL 37344, **SR 58611A**, and ICI 215001, indicated that (-)-isoprenaline can stimulate the enzyme through a relevant .beta.1-adrenergic component, while the other drugs activate the enzyme mainly by acting on the .beta.3-adrenoceptors. On the contrary, antagonism of the lipolysis yielded apparent pA2 values for CGP 20712A and ICI 118551, suggesting that (-)-isoprenaline, like all the .beta.3-adrenoceptor agonists, stimulated the brown adipose tissue lipid metab. mainly through an action on .beta.3-adrenoceptors.

IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-adrenoceptor subtypes role in cAMP accumulation and glycerol release by rat brown adipocytes)

L99 ANSWER 22 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:817700 HCAPLUS
DN 123:275737
TI Rat frontal cortex .beta.1-adrenoceptors are activated by the .beta.3-adrenoceptor agonists **SR 58611A** and SR 58878A but not by BRL 37344 or ICI 215,001

AU Nisoli, Enzo; Tonello, Cristina; Benarese, Marina; Carruba, Michele O.
CS School Medicine, Univ. Milan, Milan, Italy
SO Journal of Neurochemistry (**1995**), 65(4), 1580-7
CODEN: JONRA9; ISSN: 0022-3042
PB Lippincott-Raven
DT Journal
LA English
AB **SR 58611A**, a selective agonist of gut and brown adipose tissue .beta.3-adrenoceptors (.beta.3ARs), has been reported to have antidepressant-like activity in rodents, indicating brain .beta.3ARs as the sites of this property. **SR 58611A** and its acid metabolite SR 58878A, as opposed to BRL 37344, ICI 215,001, and CGP 12177, increased cAMP levels in rat frontal cortex. ICI 215,001, differently from BRL 37344, at concns. in the millimolar range, partially antagonized norepinephrine- or (-)-isoproterenol-stimulated adenylyl cyclase. The increase of cAMP levels induced by SR 58878A was blocked selectively by the .beta.1AR antagonist CGP 20712A but not by the .beta.2AR antagonist ICI 118,551. In addn., PCR anal. did not reveal .beta.3AR mRNA, and no specific .beta.3AR binding sites were detected by [3H]CGP 12177 in rat frontal cortex. When down-regulation of the .beta.1AR ligand binding and mRNA levels had been induced in the frontal cortex by chronic administration of imipramine, SR 58878A as well as norepinephrine and (-)-isoproterenol increased the cAMP prodn. less markedly. The findings indicate that .beta.3ARs are absent in the adult rat frontal cortex, and that various .beta.3AR agonists differently affect the frontal cortex .beta.1ARs, indicating that **SR 58611A** may exert its putative antidepressant effect by acting on the frontal cortex .beta.1ARs.
IT **121524-09-2, SR 58611A 160696-89-9,**
SR 58878A
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(brain frontal cortex .beta.1-adrenergic receptors activated by)

L99 ANSWER 23 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:794026 HCAPLUS
DN 123:246542
TI Selective activation of brown adipocyte hormone-sensitive lipase and cAMP production in the mouse by .beta.3-adrenoceptor agonists
AU Shih, Mei-Fen; Taberner, Peter V.
CS Sch. Med. Sci., Univ. Bristol, Bristol, BS8 1TD, UK
SO Biochemical Pharmacology (**1995**), 50(5), 601-8
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier
DT Journal
LA English
AB Acute injection of either noradrenaline or isoprenaline in mice activated both brown (BAT) and white (WAT) adipose tissue hormone-sensitive lipase activity (HSL). Dose-response studies indicated that isoprenaline (0.05-0.15 mg/kg) produced a dose-dependent activation of HSL in both BAT and WAT, whereas **SR 58611A** produced no change in HSL in WAT over a dose range (105 mg/kg) which, at the same time, dose-dependently increased HSL activity in BAT. The other .beta.3-adrenoceptor agonists, ZD 7114 (10 mg/kg) and BRL 35135 A (5 mg/kg) also selectively increased HSL activity in BAT, these doses having previously been shown to stimulate lipogenesis in vivo. Higher doses of ZD 7114 and BRL 35135 produced no further increase in HSL activity and, in the case of BRL 35135, provoked symptoms of non-selective .beta.-adrenoceptor activation. The increase in HSL activity could be prevented by pretreating the mice with propranolol, 10 mg/kg, i.p., 30 min prior to the agonist. The activation of HSL activity by the .beta.3-adrenoceptor agonists was assocd. with an increase in tissue cAMP prodn. which was also prevented by pretreatment with propranolol. The degree of cAMP accumulation was least with BRL 35135 and greatest with ZD

7114. The authors conclude that, in the mouse adipocyte, the atypical .beta.-adrenoceptor (.beta.3) is present in BAT, but is not present or functional in WAT.

IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(selective activation of brown adipocyte hormone-sensitive lipase and cAMP prodn. in the mouse by .beta.3-adrenoceptor agonists)

L99 ANSWER 24 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:614635 HCAPLUS
DN 123:74228
TI Predictive quantitative structure-activity relationships (QSAR) analysis of .beta.3-adrenergic ligands
AU Blin, Nathalie; Federici, Christian; Koschielniak, Thiery; Strosberg, Donny
CS Institut`Cochin Genetique Moleculaire, Universite Paris VII, Paris, 75014, Fr.
SO Drug Design and Discovery (**1995**), 12(4), 297-311
CODEN: DDDIEV; ISSN: 1055-9612
PB Harwood
DT Journal
LA English
AB A novel quant. structure-activity relationships strategy was used to analyzed seventeen .beta.-adrenergic ligands for which we had previously evaluated pharmacol. properties in Chinese hamster ovary cells transfected with the human .beta.1-, .beta.2- or .beta.3-adrenergic gene (Blin et al., 1993, Mol. Pharmacol., 44: 1094-1104). These ligands were classified into pharmacol. activity categories in order to det. the extent to which mol. structural features may be involved in the selectivity of the interaction with the .beta.3-AR, or to define mol. features and properties characteristic of a .beta.3-AR high affinity ligand or of a potent .beta.3-adrenergic agonist. Topol. and physico-chem. mol. descriptors were obtained using a novel software combining calcns. with multivariate statistical methods, such as principal component anal. and discriminant anal. This study showed that .beta.1/.beta.2-antagonists .beta.3-agonists could be differentiate from .beta.1/.beta.2/.beta.3-agonists on the basis of their topol. mol. descriptors weighted by partial at. charge and lipophilicity logP values. Bulky lipophilic groups at the end of the alkylamine chain and an ethoxy function, extending the flexible portion of the mol. and modifying the electron d. distribution, were requirements for selective agonism at the .beta.3-site. Charge and logP weighted 2D-autocorrelation vectors were properties able to discriminate between classes of agonists to terms of their affinity, potency or intrinsic activity, thus emphasizing the part these mol. descriptors play in detg. .beta.3-adrenergic ligands. These results, in assocn. with the powerful activity-prediction model evaluated in the test, provide a framework to rationalize the synthesis of new .beta.3-AR specific compds.

IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(QSAR anal. of .beta.3-adrenergic ligands)

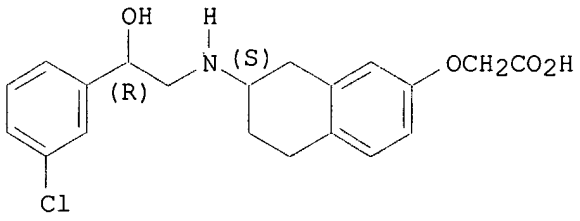
L99 ANSWER 25 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:494286 HCAPLUS
DN 122:256840
TI Inhibitory effects of **SR 58611A** on canine colonic motility: evidence for a role of .beta.3-adrenoceptors
AU de Ponti, Fabrizio; Cosentino, Marco; Costa, Angela; Girani, Marco; Gibelli, Graziano; d'Angelo, Luigi; Frigo, Gianmario; Crema, Antonio
CS Dep. Internal Med. and Therapeutics, Univ. Pavia, Pavia, I-27100, Italy
SO British Journal of Pharmacology (**1995**), 114(7), 1447-53

CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB To clarify whether atypical of .beta.3-adrenoceptors can modulate canine colonic motility in vivo, we studied the effects of **SR 58611A** (a selective agonist for atypical .beta.-adrenoceptors) alone and after pretreatment with .beta.-adrenoceptor antagonists on colonic motility in the conscious dog. The gastrocolonic response (postprandial increase in motility) was monitored by electrodes and strain-gauge force transducers chronically implanted along the distal colon. In some expts., heart rate was also measured. The possible role of .beta.3-adrenoceptors in mediating the effects of **SR 58611A** was also tested in vitro in circular muscle strips taken from the canine distal colon. I.v. infusion of **SR 58611A**, ritodrine or isoprenaline at doses inducing the same degree of tachycardia inhibited the gastrocolonic response to a different extent, with **SR 58611A** and ritodrine being more effective than isoprenaline. In a dose-response study, **SR 58611A** was more potent in inhibiting colonic motility than in inducing tachycardia: the ED35 values for inhibition of colonic motility and induction of tachycardia were 23 and 156 .mu.g kg-1, i.v., resp. The inhibitory effect of **SR 58611A** 100 .mu.g kg-1, i.v., on the gastrocolonic response was reversed by alprenolol (non-selective .beta.-adrenoceptor antagonist), but resistant to CGP 20712A (.beta.1-adrenoceptor antagonist) or ICI 118551 (.beta.2-adrenoceptor antagonist). In vitro, **SR 58611A** concn.-dependently relaxed circular muscle strips, an effect that was competitively antagonized by alprenolol with a pA2 values of 7.1, but resistant to CGP 20712A (100 nM), ICI 118551 (100 nM) or tetrodotoxin (1 .mu.m). The present study provides strong functional evidence for a role of atypical or .beta.3-adrenoceptors in the modulation of canine colonic motility both in vivo and in vitro by an inhibitory effect most likely at the smooth muscle level.
IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitory effects of **SR 58611A** on canine colonic motility and evidence for a role of ~~.beta.3-adrenoceptors~~)

L99 ANSWER 26 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:347146 HCAPLUS
DN 122:132788
TI Preparation of (7S)-7-(1R)-2-(3-chlorophenyl)-2-hydroethylamino-5,6,7,8-tetrahydronaphtalen-2-yloxyacetic acid .beta.3-adrenergic agonist and pharmaceutical compositions containing it
IN Baroni, Marco; Cecchi, Roberto; Croci, Tiziano
PA Sanofi, Fr.; Midy S.P.A.
SO Eur. Pat. Appl., 6 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 626367	A1	19941130	EP 1994-401163	19940526 <--
	EP 626367	B1	19970409		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	EP 627407	A1	19941207	EP 1993-401375	19930528 <--
	R: IT				
PRAI	EP 1993-401375		19930528 <--		

GI



I

AB The title compd., I [m.p. 215.degree., decompn.; [.alpha.]20 = -98.4.degree. (0.5% MeOH/HCl 1N)], and its pharmaceutically acceptable salts (e.g., the Na salt) is prepd. by the sapon. of the corresponding Et ester and is useful as a .beta.3-adrenergic receptor agonist for the treatment of diseases amenable to application of a .beta.3-adrenergic agonist [e.g., irritable colon (no data), obesity (no data), anxiety (no data), etc. (no data)].

IT **160696-89-9DP**, salts **160853-47-4P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed; prepn. as .beta.3-adrenergic receptor agonist)

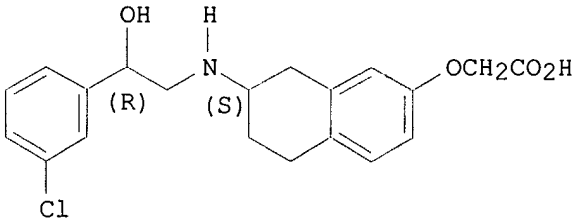
IT **160696-89-9P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. as .beta.3-adrenergic receptor agonist)

IT **121524-08-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of (7S)-7-(1R)-2-(3-chlorophenyl)-2-hydroethylamino-5,6,7,8-tetrahydronaphtalen-2-yloxyacetic acid .beta.3-adrenergic agonist and pharmaceutical compns. contg. it)

L99 ANSWER 27 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:331108 HCAPLUS
DN 122:105454
TI Preparation of (7S)-7-[[2(3-chlorophenyl)-2-hydroxyethylamino]-5,6,7,8-tetrahydronaphthalen-2-yloxy]acetic acid .beta.3-adrenergic receptor agonist
IN Baroni, Marco; Croci, Tiziano; Cecchi, Roberto
PA Miday s.p.a., Italy
SO Eur. Pat. Appl., 5 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 627407	A1	19941207	EP 1993-401375	19930528 <--
	R: IT				
	EP 626367	A1	19941130	EP 1994-401163	19940526 <--
	EP 626367	B1	19970409		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	AT 151405	E	19970415	AT 1994-401163	19940526 <--
	ES 2103113	T3	19970816	ES 1994-401163	19940526 <--
	JP 07070013	A2	19950314	JP 1994-117182	19940530 <--
	US 5488151	A	19960130	US 1994-250830	19940531 <--
PRAI	EP 1993-401375		19930528 <--		

GI



I

AB The title compd., I, prepd. by the basic hydrolysis of the corresponding I Et ester, is prepd. and useful as a .beta.3-adrenergic receptor agonist (no data) for use as an antiobesity agent (no data), for the treatment of gastrointestinal problems due to the G.I. contraction of smooth muscle (no data), for the treatment of irritable colon (no data), etc. (no data).

IT **160696-89-9DP**, salts **160696-89-9P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. as .beta.3-adrenergic receptor agonist)

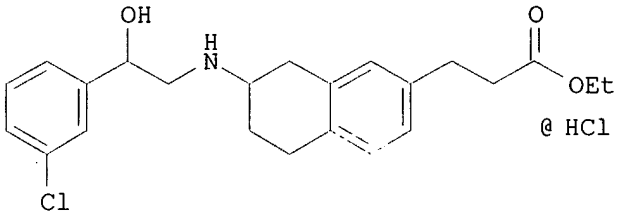
IT **121524-08-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of .beta.3-adrenergic receptor agonist by hydrolysis of)

L99 ANSWER 28 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:215093 HCAPLUS
DN 122:741
TI .beta.3-Adrenoceptor agonists, BRL 37344 and **SR 58611A**, do not induce relaxation of human, sheep and guinea pig airway smooth muscle in vitro
AU Martin, C.A.E.; Naline, E.; Bakdach, H.; Advenier, C.
CS Laboratoire de Pharmacologie, Faculte de Medecine Paris-Ouest, Paris, F-75270, Fr.
SO European Respiratory Journal (**1994**), 7(9), 1610-15
CODEN: ERJOEI; ISSN: 0903-1936
DT Journal
LA English
AB The existence of atypical- or .beta.3-adrenoceptors has now been generally accepted. These receptors have been shown to be abundant in adipose tissue and in a no. of gastrointestinal smooth muscle prepns. A recent study reported that .beta.3-adrenoceptor stimulation mediated relaxation of isolated canine bronchial smooth muscle. The aim of the present study was to extend this observation to other species. The authors investigated the in vitro responses of guinea-pig, human and sheep bronchial smooth muscle to isoprenaline, salbutamol (a selective .beta.2-adrenoceptor agonist), and BRL 37344 and **SR 58611A** (two presumably selective .beta.3-adrenoceptor agonists). The prepns. were precontracted to 60-70% of maximal tension with histamine 10-6 M for guinea-pig and human bronchi, or acetylcholine 10-6 M for sheep bronchi. In each species, **SR 58611A** produced a slight fall in tension of about 10% of the effects of theophylline (3 mM), but this decrease in tension was not significantly different from the spontaneous and weak relaxation obsd. with saline addn. during the same duration of the expt. These relaxations were not modified by either the nonselective .beta.-adrenoceptor antagonist propranolol or the selective .beta.2-adrenoceptor antagonist ICI 118,551. In contrast, BRL 37344 induced a significant concn.-dependent fall in tension induced by both spasmogens. Its relaxant effects were inhibited both by propranolol and ICI 118,551 in human and guinea-pig airways, whereas on the isolated sheep bronchus BRL 37344-induced relaxations were only slightly, albeit significantly, reduced with either of the .beta.-adrenoceptor antagonists

tested. Salbutamol and isoprenaline induced potent relaxations of guinea-pig, human and sheep airway smooth muscle in vitro, which were antagonized both by propranolol and ICI 118,551. The authors findings show that .beta.3-adrenoceptor stimulation does not induce relaxation in guinea-pig, human and sheep bronchial smooth muscle, and that a .beta.2-adrenoceptor agonistic component might be implicated in the relaxant effects of BRL 37344.

IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.3-adrenoceptor agonists BRL 37344 and **SR 58611A** do not induce relaxation of human, sheep, and guinea pig airway smooth muscle in vitro)

L99 ANSWER 29 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:63848 HCAPLUS
DN 122:80821
TI Synthesis of the potent and selective atypical .beta.-adrenergic agonist SR 59062 A
AU Badone, Domenico; Guzzi, Umberto
CS Res. Cent., Sanofi-Midy SpA, Milan, Italy
SO Bioorganic & Medicinal Chemistry Letters (**1994**), 16(4), 1921-4
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
GI



I

AB The search for synthesis and evaluation of a novel highly potent atypical .beta.-adrenergic agonist (.beta.3-agonist) are described. An example compd. is the SR 68611A analog 7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenepropanoate hydrochloride (I) (diastereomers).

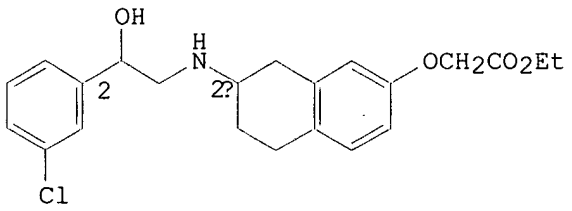
IT **121524-09-2, SR 58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); MSC (Miscellaneous); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(prepn. of SR 59062A (**SR 58611A** bioisostere))

L99 ANSWER 30 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:645501 HCAPLUS
DN 121:245501
TI Enhancement of gastric mucosal blood flow by beta-3 adrenergic agonists prevents indomethacin-induced antral ulcer in the rat
AU Kuratani, Kazuyoshi; Kodama, Hiroshi; Yamaguchi, Isamu
CS Tsukuba Res. Labs., Fujisawa Pharm. Co. Ltd., Tsukuba, 300-26, Japan
SO Journal of Pharmacology and Experimental Therapeutics (**1994**), 270(2), 559-65
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB Indomethacin (32 mg/kg s.c.) produced mainly antral ulcers in refed rats

but almost exclusively corpus erosions in fasted rats. S.c. doses of a nonselective beta (isoproterenol), a selective .beta.-2 (salbutamol) and selective .beta.-3 adrenergic agonists BRL 35135, CL 316243, **SR 58611A**, dose-dependently attenuated the antral ulcers, and their activities were in the order of BRL 35135 (ED50 = 0.03 mg/kg) > CL 316243 (ED50 = 0.04 mg/kg) > SR 68511A (ED50 = 0.2 mg/kg) > isoproterenol (ED50 = 0.4 mg/kg) > salbutamol (ED50 = 6 mg/kg). Whereas only isoproterenol, salbutamol and BRL35135 significantly attenuated the corpus erosions and reduced gastric acid secretion in pylorus-ligated rats. In in vitro, all the beta agonists enhanced the beating rate of guinea pig atria (.beta.-1 action) and inhibited spontaneous contractions of rat uterus (.beta.-2 action) and colon (.beta.-3 action). There was found a statistically significant correlation between the IC50 values of the drugs on the colon and ED50 values on the indomethacin-induced antral ulcers (r = 0.97). In addn., the beta agonists excepting salbutamol increased antral gastric mucosal blood flow in rats anesthetized with halothane, and the activities were arranged in the potency order of inhibiting colon motility. It is concluded that activation of .beta.-3 adrenoceptor attenuates the indomethacin-induced antral ulcers through an enhancement of antral gastric mucosal blood flow, whereas activation of beta-1 and/or .beta.-2 adrenoceptors attenuates indomethacin-induced corpus erosions through an inhibition of gastric secretion.

IT **121524-09-2, SR58611A**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(enhancement of gastric mucosal blood flow by beta-3 adrenergic agonists prevents indomethacin-induced antral ulcer in rat)

L99 ANSWER 31 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:630444 HCAPLUS
DN 121:230444
TI Synthesis and .beta.-adrenergic activity of atypical .beta.-adrenergic phenylethanolaminotetralin stereoisomers
AU Cecchi, R.; Croci, T.; Boigegrain, R.; Boveri, S.; Baroni, M.; Boccardi, G.; Guimbard, J. P.; Guzzi, U.
CS Res. Cent., Sanofi Midy SpA, Milan, 20137, Italy
SO European Journal of Medicinal Chemistry (**1994**), 29(4), 259-67
CODEN: EJMCA5; ISSN: 0223-5234
DT Journal
LA English
OS CASREACT 121:230444
GI



I

AB A series of substituted phenylethanolaminotetralins were synthesized as pure stereoisomers and their ability to stimulate atypical .beta.-adrenoceptors selectively was evaluated. The compds. in vitro relative potencies were assessed using the atypical .beta. response of inhibition of rat proximal colon motility and the typical .beta.1 (increase in guinea-pig right atrial frequency) and .beta.2 (guinea-pig tracheal relaxation and rat uterus motility inhibition) responses. (2R,2'S)-I (SR 58611A) was found to be the most potent and selective.

IT **121216-31-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and conversion of, to adrenergic phenylethanolaminotetralin stereoisomer)
IT **107758-36-1P 107758-37-2P 107758-38-3P 107758-39-4P 120839-53-4P 121216-32-8P 158223-17-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and .beta.-adrenergic activity of)

L99 ANSWER 32 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:549595 HCAPLUS
DN 121:149595
TI .beta.-Adrenergic control of lipolysis in primate white fat cells: a comparative study with nonprimate mammals
AU Bousquet-Melou, Alain; Galitzky, Jean; Carpene, Christian; Lafontan, Max; Berlan, Michel
CS Faculte de Medecine, Universite Paul Sabatier, Toulouse, 31073, Fr.
SO American Journal of Physiology (**1994**), 267(1, Pt. 2), R115-R123
CODEN: AJPHAP; ISSN: 0002-9513
DT Journal
LA English
AB The .beta.-adrenoceptor subtypes involved in the control of lipolysis in white fat cells of rat, dog, marmoset (Callithrix jacchus), baboon (Papio papio), macaque (Macaca fascicularis), and human were compared. In all species, [3H]CGP-12177 binding (up to 3 nM) indicated the existence of a homogeneous population of binding sites in fat cell membranes, and competition studies showed that .beta.1- and .beta.2-adrenoceptors were present. Selective .beta.1- or .beta.2-adrenoceptor agonists induced lipolysis. The efficiencies of isoproterenol and norepinephrine were similar. The use of selective .beta.3-adrenoceptor agonists revealed that BRL-37344 and CL-316243 were full agonists, whereas CGP-12177 and **SR-58611A** were partial agonists in rat and dog white fat cells. .beta.3-Agonists partially stimulated lipolysis in the marmoset, while CGP-12177 was weakly active in the baboon. In macaque and human fat cells, B3-agonists were ineffective. The lipolytic effect of norepinephrine involves .beta.1-and/or .beta.2-adrenoceptors in baboon, macaque, and human. The baboon and macaque constitute valuable models for studying the .beta.-adrenergic control of lipolysis.
IT **121524-09-2, SR-58611A**
RL: BIOL (Biological study)
(lipolysis stimulation by, in adipose tissue of human and mammals)

L99 ANSWER 33 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:473752 HCAPLUS
DN 121:73752
TI **SR 58611A**: a novel thermogenic .beta.-adrenoceptor agonist
AU Nisoli, Enzo; Tonello, Cristina; Carruba, Michele O.
CS Section of Pharmacology, Toxicology and Experimental Therapeutics, Department of Biomedical Sciences and Biotechnologies, School of Medicine, University of Brescia, Via Valsabbina 19, Brescia, 25123, Italy
SO European Journal of Pharmacology (**1994**), 259(2), 181-6
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB N(2S)-7-[carbethoxymethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine hydrochloride (**SR 58611A**) increased cAMP levels in membrane homogenates from rat interscapular brown adipose tissue with an EC50 of 20 nM. Substitution of GTP with the GDP analog, guanosine-5'-O-[thiodiphosphate], in the incubation medium suppressed the stimulation of adenylyl cyclase activity by **SR 58611A**. This compd. also stimulated glycerol release from the

brown fat cells, with an EC50 of 11 nM. Only at doses higher than 10 .mu.M did the non-selective .beta.-adrenoceptor antagonists, propranolol and alprenolol, as well as the selective .beta.1- and .beta.2-adrenoceptor antagonists, (.+-.)-[2-(3-carbamoyl-4-hydroxyphenoxy)-ethylamino]-3-[4(1-methyl-4-trifluoromethyl-2-imidazolyl)-phenoxy]-2 propanol (CGP 20712A) and erythro-(.+-.)-1-(7-methylindan-4-yloxy)-3-iso-propylaminobutan-2-ol-hydrochloride (ICI 118,551), antagonize the **SR 58611A** -induced stimulation of both adenylyl cyclase activity and lipid metab. Since, at high doses, all these .beta.- adrenoceptor antagonists lack selectivity for .beta.1- or .beta.2- adrenoceptors, these results suggest that the .beta.-adrenoceptor agonist, **SR 58611A**, activates thermogenesis by acting on brown fat cell .beta.3-adrenoceptors. This implies that this compd. might be useful for treatment of obesity.

IT **121524-09-2, SR 58611A**
RL: BIOL (Biological study)
(thermogenesis from, adipose tissue metab. in, antiobesity activity in relation to)

L99 ANSWER 34 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:153732 HCAPLUS
DN 120:153732
TI Atypical .beta.-adrenoceptor agonists for treatment of gastrointestinal disorders
IN Bahl, Ashwani K.
PA Glaxo Group Ltd., UK
SO Can. Pat. Appl., 29 pp.
CODEN: CPXXEB
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	CA 2087823	AA	19930723	CA 1993-2087823	19930121	<--
	EP 556880	A2	19930825	EP 1993-200096	19930115	<--
	EP 556880	A3	19931027			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
	EP 713698	A2	19960529	EP 1995-202209	19930115	<--
	EP 713698	A3	19960612			
	EP 713698	B1	20020403			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
	AT 215365	E	20020415	AT 1995-202209	19930115	<--
	AU 9331981	A1	19930729	AU 1993-31981	19930121	<--
	AU 666904	B2	19960229			
	JP 05255114	A2	19931005	JP 1993-8603	19930121	<--
	ZA 9300424	A	19931011	ZA 1993-424	19930121	<--
	IL 104464	A1	19970930	IL 1993-104464	19930121	<--
PRAI	GB 1992-1359	A	19920122	<--		
	GB 1992-25684	A	19921209	<--		
	EP 1993-200096	A3	19930115	<--		

OS MARPAT 120:153732
AB Agonists (Markush included) of atypical .beta.-adrenoceptors are used for treating gastrointestinal disorders, esp. peptic ulceration, esophagitis, gastritis and duodenitis, intestinal ulcerations, including inflammatory bowel disease, and gastrointestinal ulcerations, esp. when induced by nonsteroidal antiinflammatory drugs or corticosteroids. Fifteen specific agonists are claimed. Thus, in animal studies, CL316243 [(R,R)-5-(2-((2-(3-chlorophenyl)-2-hydroxyethyl)amino)propyl)-1,3-benzodioxole-2,2-dicarboxylic acid] showed 83 and 96% inhibition of indomethacin-induced and piroxicam-induced gastrointestinal damage, resp. Tablet, syrup, i.v. injection, and suppository formulations are included.

IT **107758-23-6**, SR 58572 **107758-27-0**, SR 58380
107758-43-0, SR 58306 **121524-08-1, SR 58611**

RL: BIOL (Biological study)
(as agonist of atypical .beta.-adrenoceptor, for gastrointestinal disorder treatment)

L99 ANSWER 35 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:95485 HCAPLUS
DN 120:95485
TI Effects of two .beta.3-adrenoceptor agonists, **SR 58611A** and BRL 37344, and of salbutamol on cholinergic and NANC neural contraction in guinea pig main bronchi in vitro
AU Martin, Corinne A. E.; Naline, Emmanuel; Manara, Luciano; Advenier, Charles
CS Dep. Pharmacol., Fac. Med. Paris-Ouest, Paris, F-75270, Fr.
SO British Journal of Pharmacology (**1993**), 110(4), 1311-16
CODEN: BJPCBM; ISSN: 0007-1188
DT Journal
LA English
AB The aim of the present study was to investigate the type of adrenoceptor which modulates constriction of the guinea-pig isolated main bronchus in response to elec. field stimulation (EFS). Drugs used were salbutamol and two agonists reportedly selective for the putative .beta.3-adrenoceptor: BRL 37344 and **SR 58611A**. At basal tone, all three drugs induced relaxation, however, **SR 58611A** and BRL 37344 (10-9 to 10-6 M) relaxed guinea-pig isolated main bronchus more weakly than salbutamol (10-9 to 10-6 M). The effects obsd. at 10-6 M were 43% .+-. 9%, 63% .+-. 4% and 98% .+-. 1% of the maximal effect induced by theophylline (3 .times. 10-3 M) for **SR 58611A**, BRL 37344 and salbutamol, resp. **SR 58611A** and BRL 37344 (10-8 to 10-6 M) did not significantly modify the cholinergic component of the response to EFS, but caused a concn.-dependent redn. of the nonadrenergic noncholinergic (NANC) excitatory component (41.8% .+-. 10.1% and 56.8% .+-. 7.4% resp. at 10-6 M, n = 6-7). Salbutamol (10-9 to 10-7 M) strongly inhibited both components, with 91.1% .+-. 4.2% of inhibition for the NANC contraction and 62.0% .+-. 5.2% of inhibition for the cholinergic contraction (10-7 M, n = 7). Whereas the inhibitory effects of salbutamol were strongly inhibited by both propranolol (10-6 M) and ICI 118,551 (10-6 M), those of BRL 37344 were only slightly, albeit significantly reduced by both propranolol and ICI 118,551, and those of **SR 58611A** were unaffected by treatment with either .beta.-adrenoceptor antagonist. An .alpha.2-adrenoceptor antagonist, yohimbine, did not influence the inhibitory effects of any of the .beta.-adrenoceptor agonists tested. Concn.-response curves to acetylcholine (10-8 to 10-3 M), [Nle10]NKA(4-10) (10-10 to 10-6 M) and substance P (10-10 to 3 .times. 10-6 M) were also significantly shifted to the right by salbutamol (10-6 M), whereas **SR 58611A** and BRL 37344 (10-6 M) had no effect. These results suggest that the stimulation of putative .beta.3-adrenoceptors exerts a specific prejunctional inhibitory action on NANC excitatory response induced by EFS of the isolated main bronchus of the guinea-pig. They also suggest that a .beta.2-adrenoceptor agonistic component may be involved in the effects of BRL 37344.
IT **121524-09-2, SR 58611A**
RL: BIOL (Biological study)
(cholinergic and NANC neural contraction in main bronchi response to, as .beta.3-adrenoceptor agonist)

L99 ANSWER 36 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1993:663143 HCAPLUS
DN 119:263143
TI Similar atypical .beta.-adrenergic receptors mediate in vitro rat adipocyte lipolysis and colonic motility inhibition
AU Landi, Marco; Croci, Tiziano; Manara, Luciano
CS Res. Cent., SANOFI-MIDY S.p.A., Milan, 20137, Italy

SO Life Sciences (**1993**), 53(18), PL297-PL302
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
AB The authors studied the putative common nature of the rat atypical .beta.-adrenoceptors mediating white adipocyte lipolysis and proximal colon motility inhibition, using the nonselective antagonist alprenolol and agonist isoprenaline and the selective agonists **SR 58611A** and BRL 37344. Results in either isolated intestinal and fat tissues were consistent with: isoprenaline acting through both typical (.beta.1, .beta.2) and atypical .beta.-adrenoceptors; **SR 58611A** and BRL 37344 acting solely through the latter. The identical pA2 values obtained with alprenolol, irresp. of the tissue and the selective agonist (**SR 58611A** or BRL 37344) used, support the high functional homol. of the atypical .beta.-adrenoceptors in rat colon and adipocytes.
IT **121524-09-2, SR 58611A**
RL: BIOL (Biological study)
(adipocyte lipolysis and colonic motility response to, .beta.-adrenergic receptors mediation of)

L99 ANSWER 37 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:585365 HCAPLUS
DN 117:185365
TI Phenylethanolaminotetralines compete with [3H]dihydroalprenolol binding to rat colon membranes without evidencing atypical .beta.-adrenergic sites
AU Landi, Marco; Bianchetti, Alberto; Croci, Tiziano; Manara, Luciano
CS Res. Cent., Sanofi-Midy S.p.A., Milan, 20137, Italy
SO Biochemical Pharmacology (**1992**), 44(4), 665-72
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB [3H]Dihydroalprenolol ([3H]DHA)-specific binding (detd. by the difference in the presence and absence of 20 .mu.M (-)isoprenaline) to rat colon membranes was saturable (Bmax = 39.6 fmol/mg protein), of high affinity (Kd = 0.87 nM), and stereospecific (IC50 330 and 3510 nM for (-)- and (+)isoprenaline, resp.); the Hill coeff. was close to one, indicating binding homogeneity. [3H]DHA (0.6 nM) specific binding was potently inhibited (Ki range 1.9-3.3 nM) by the non-selective .beta.-adrenoceptor antagonists pindolol, alprenolol, and propranolol, but not by the nonadrenergic compds. 5-hydroxytryptamine, 8-hydroxydipropylaminotetraline , methylsergide, dopamine, and verapamil (Ki >10,000 nM). The selective .beta.1- and .beta.2-adrenoceptor antagonists CGP 20,712A and ICI 118,551 resulted in biphasic competition binding curves, whose low and high affinity components were compatible with two populations of binding sites accounting for about 75 (.beta.2) and 25% (.beta.1) of total sites. The relative competing potencies of ref. adrenergic agonists also suggested a prevalence of .beta.2-adrenergic sites. The new agonists phenylethanolaminotetralines (PEATs), highly selective for the atypical .beta.-adrenoceptors whose abundance in rat colon has been confirmed by comprehensive functional studies, had variable affinity for the [3H]DHA-labeled sites depending on chirality, but with no substantial correlation with their pharmacol. potency. Only 40% of [3H]DHA binding, at a concn. about 10 times its Kd for high affinity sites (.beta.1 and .beta.2), was prevented by satg. concns. of isoprenaline. Under this condition, the representative PEAT, SR 58611A, highly potent and selective for atypical .beta.-adrenoceptors in functional tests, and its pharmacol. inactive enantiomer, both inhibited the residual binding equipotently. In conclusion, [3H]DHA binding did not detect atypical .beta.-adrenoceptor sites in rat colon membranes, most probably because of its weaker affinity for them than for the coexisting .beta.1 and .beta.2 sites. PEAT stereoisomers proved essential for assessing both the stereospecificity and the functional significance of this atypical binding and to compare

their affinity for [3H]DHA-labeled sites and pharmacol. potency.
IT **107758-36-1**, SR 58375A **107758-37-2**, SR 58374A
107758-39-4, SR 58373A **107758-41-8**, SR 58372
120839-53-4, SR 58572A **121216-30-6**, SR 58590
121216-31-7, SR 58589 **121216-32-8**, SR 58575A
RL: BIOL (Biological study)
(dihydroalprenolol binding by colon membranes displacement by)

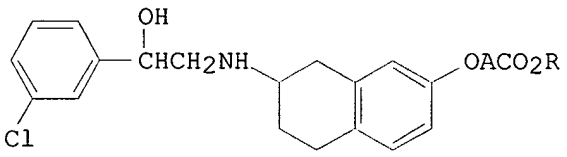
L99 ANSWER 38 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:584788 HCAPLUS
DN 117:184788
TI Antidepressant profile in rodents of **SR 58611A**, a new selective agonist for atypical .beta.-adrenoceptors
AU Simiand, Jacques; Keane, Peter E.; Guitard, Josette; Langlois, Xavier; Gonalons, Nadine; Martin, Patrick; Bianchetti, Alberto; Le Fur, Gerard; Soubrie, Philippe
CS Sanofi Rech., Toulouse, 31036, Fr.
SO European Journal of Pharmacology (**1992**), 219(2), 193-201
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB .beta.2-Adrenoceptor agonists possess antidepressant-like activity in animals and man, but their peripheral side-effects prevent their therapeutic use. Atypical .beta.-adrenoceptors have not been found in the central nervous system, but exist in peripheral tissues such as the rat colon. The antidepressant-like effects of **SR 58611A** were studied in mice and rats. **SR 58611A** was active with minimal EDs of 0.1-0.3 mg/kg i.p. in several models (antagonism of hypothermia induced by apomorphine and reserpine, potentiation of yohimbine toxicity, reversal of learned helplessness), but was inactive in the tests of reserpine-induced ptosis and behavioral despair. The antidepressant-like effect of **SR 58611A** was not antagonized by selective .beta.1- or .beta.2-adrenergic receptor antagonists, but was blocked by high doses of the non-selective .beta.-adrenoceptor antagonists propranolol and alprenolol. Unlike .beta.2-adrenoceptor agonists, **SR 58611A** did not reduce the locomotor activity or increase the water intake at doses up to 10 mg/kg. **SR 58611A** is a prototype of a new class of antidepressant compds.
IT **121524-09-2**
RL: BIOL (Biological study)
(antidepressant pharmacol. of, atypical .beta.-adrenergic receptors role in)

L99 ANSWER 39 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:563882 HCAPLUS
DN 117:163882
TI Phenylethanolaminotetralins as antidepressant and antistress agents
IN Keane, Peter Eugene; Bianchetti, Alberto; Simiand, Jacques; Croci, Tiziano
PA Elf Sanofi, Fr.
SO Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	EP 489640	A1	19920610	EP 1991-403263	19911203	<--
	EP 489640	B1	19961002			
	R: AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE					
	FR 2669821	A1	19920605	FR 1990-15171	19901204	<--
	FR 2669821	B1	19941209			
	AT 143592	E	19961015	AT 1991-403263	19911203	<--

CA 2056906	AA	19920605	CA 1991-2056906	19911204	<--
CA 2056906	C	19980428			
AU 9188395	A1	19920611	AU 1991-88395	19911204	<--
AU 653968	B2	19941020			
HU 59595	A2	19920629	HU 1991-3800	19911204	<--
HU 207793	B	19930628			
JP 05025040	A2	19930202	JP 1991-320532	19911204	<--
US 5270341	A	19931214	US 1991-804580	19911204	<--

PRAI FR 1990-15171 19901204 <--
OS MARPAT 117:163882
GI



I

AB The title compds. I (A = C1-4 alkylene; R = H, C1-4 alkyl) are drugs for the prevention and treatment of depression and stress. Oral administration of N-[(2S)7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine-HCl (2 mg/kg) lowered the myoelec. activity of the proximal colon in rats under immobilization stress.

IT **121524-10-5 121524-11-6 129831-97-6**
135025-87-5 143554-26-1 143554-27-2
RL: BIOL (Biological study)
(antidepressant and antistress agent)

L99 ANSWER 40 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:483203 HCAPLUS
DN 117:83203
TI Stimulation of bicarbonate secretion by atypical .beta.-receptor agonists in rat cecum in vitro
AU Canfield, Paul; Abdul-Ghaffar, Tarik
CS Med. Sch., St. Mary's Hosp., London, W2 1PG, UK
SO European Journal of Pharmacology (**1992**), 216(2), 293-7
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB This study examd. the effects of .beta.-adrenoceptor agonists on bicarbonate secretion by the rat cecum in vitro. Isoprenaline, the .beta.2-selective agonist salbutamol and the 'atypical' .beta.-agonist **SR58611A** stimulated bicarbonate secretion in a concn. related manner. Another atypical agonist, BRL 37344, also stimulated. Responses to isoprenaline were antagonized by alprenolol and propranolol (both 20 .mu.M) but not the selective antagonists practolol (10 .mu.M) or ICI 1185511 (1 .mu.M). Responses to **Sr 58611A** were only antagonized by alprenolol. Replacement of Cl- by NO3- on the mucosal surface reduced basal secretion and abolished the response to isoprenaline. Exposure to a single concn. of atypical agonist resulted in desensitization to a second application and to isoprenaline. There was no evidence of desensitization with isoprenaline or salbutamol. The results show that .beta.-adrenoceptor agonists stimulated bicarbonate secretion in contrast to the previously described inhibitory effect of cholinergic drugs in this tissue. Stimulation was mediated by .beta.-adrenoreceptors, which had properties consistent with the atypical receptors described in gut smooth muscle and in adipose tissue. Both adrenergic and cholinergic drugs may act on the same mechanism of secretion which may involve an

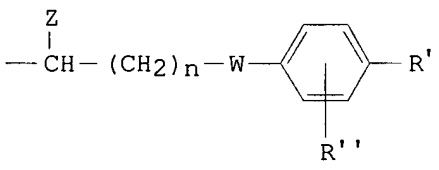
exchange of HCO3- for mucosal Cl-.

IT **121524-09-2, SR 58611A**
RL: BIOL (Biological study)
(cecum bicarbonate secretion response to)

L99 ANSWER 41 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1991:457179 HCAPLUS
DN 115:57179
TI Use of phenylethanolamines for the preparation of a medicament for treating ophthalmologic disorders, especially glaucoma
IN Manara, Luciano
PA SANOFI, Fr.; Midy S.p.A.
SO Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 403360	A2	19901219	EP 1990-401606	19900612 <--
	EP 403360	A3	19920226		
	EP 403360	B1	19961016		
	R: AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE				
	FR 2648042	A1	19901214	FR 1989-7816	19890613 <--
	FR 2648042	B1	19940610		
	FR 2648043	A1	19901214	FR 1989-7817	19890613 <--
	FR 2648043	B1	19940722		
	US 5236951	A	19930817	US 1990-536741	19900612 <--
	AT 144139	E	19961115	AT 1990-401606	19900612 <--
	JP 03031212	A2	19910212	JP 1990-154967	19900613 <--
	JP 2844109	B2	19990106		
	US 5312961	A	19940517	US 1992-905483	19920629 <--
PRAI	FR 1989-7816		19890613 <--		
	FR 1989-7817		19890613 <--		
	FR 1989-1910		19890214 <--		
	US 1990-480207		19900214 <--		
	EP 1990-401606		19900612 <--		
	US 1990-622964		19901206 <--		

OS MARPAT 115:57179
GI



Q

AB Phenylethanolamine derivs. ACH(OX)CH2N(Y)T [A = benzofuran-2-yl, (un)substituted Ph; X = H, lower alkyl, lower alkanoyl; Y = H, A1CH(OH)CH2 (A1 = (un)substituted Ph), or XY = (lower carbalkoxy-substituted) CH2, (oxo-substituted) CH2CH2, 1,3-propylene; T = Q (n = 1-3; W = bond, O; Z = H, lower alkyl; R' = H, lower alkyl, OH, lower alkoxy, etc.; R'' = H, halo, lower alkyl, etc.), etc. (with provisions)], and their pharmaceutically acceptable salts, are provided for prepn. of ophthalmic pharmaceuticals for treatment of e.g. glaucoma. Thus, an ophthalmic soln. contained N-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-(3-chlorophenyl)-2-hydroxyethanamine HCl (I) 1.0, NaH2PO4 10.4,

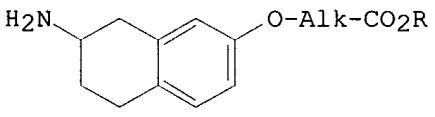
Na2HPO4 2.4, chlorobutanol 5.0, hydroxypropylmethyl cellulose 5.0 mg, 1N NaOH to pH 7.4, and water to 1.0 mL. I was tested in an exptl. (rabbit) glaucoma model.

IT **107758-23-6 121216-30-6 121489-39-2**
121489-40-5 121524-07-0 121524-08-1
129831-97-6 132990-67-1 132990-74-0
135025-87-5 135025-88-6 135025-89-7
RL: BIOL (Biological study)
(ophthalmic pharmaceutical contg., for glaucoma treatment)

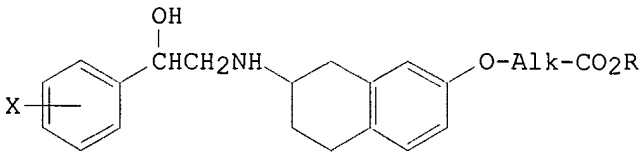
L99 ANSWER 42 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1991:185045 HCAPLUS
DN 114:185045
TI Preparation of 2-amino-7-hydroxytetralin carboxyalkyl ethers as intermediates for spasmolytic phenylethanolaminotetralins
IN Guzzi, Umberto; Cecchi, Roberto
PA SANOFI, Fr.; Midy S.p.A.
SO Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	EP 383686	A1	19900822	EP 1990-400405	19900214	<--
	EP 383686	B1	19930804			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL					
	FR 2643076	A1	19900817	FR 1989-1910	19890214	<--
	FR 2643076	B1	19910621			
	CA 2009992	AA	19900814	CA 1990-2009992	19900214	<--
	AU 9049786	A1	19900823	AU 1990-49786	19900214	<--
	AU 642402	B2	19931021			
	ZA 9001121	A	19901128	ZA 1990-1121	19900214	<--
	JP 03014548	A2	19910123	JP 1990-33584	19900214	<--
	JP 2852681	B2	19990203			
	AT 92470	E	19930815	AT 1990-400405	19900214	<--
	ES 2060079	T3	19941116	ES 1990-400405	19900214	<--
PRAI	FR 1989-1910		19890214	<--		
	EP 1990-400405		19900214	<--		

OS CASREACT 114:185045; MARPAT 114:185045
GI



I



II

AB Aminohydroxytetralin ethers I (Alk = C3-5 straight or branched alkylene; R = H, C1-4 alkyl) were prepd. as intermediates for spasmolytic (no data) phenylethanolaminotetralins II (X = H, halo, C1-4 alkyl, CF3). For example, alkylation of 2-benzylamino-7-hydroxytetralin by Br(CH2)5CO2Et

using NaH in PhMe, followed by salification with HCl(g) in Me2CHOH, and then hydrogenolysis over Pd/C in EtOH at 60.degree., gave I.HCl [Alk = (CH2)5, R = Et]. This was neutralized and coupled with 3-chlorostyrene oxide in Me2SO in the presence of N-(trimethylsilyl)acetamide at 80.degree. to give, after chromatog. and salification, II.HCl (Alk and R as above; X = 3-Cl).

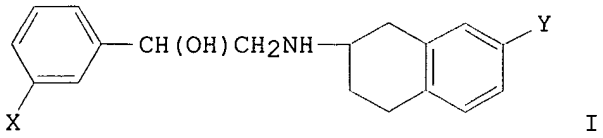
IT **132990-64-8P 132990-65-9P 132990-66-0P**
132990-67-1P 132990-68-2P 132990-69-3P
132990-74-0P 132990-75-1P 132990-76-2P
132990-77-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as spasmolytic)

L99 ANSWER 43 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1990:565225 HCAPLUS
DN 113:165225
TI In vitro inhibition of intestinal motility by phenylethanolaminotetralines: evidence of atypical .beta.-adrenoceptors in rat colon
AU Bianchetti, Alberto; Manara, Luciano
CS Res. Cent., Sanofi-Midy S.p.A., Milan, 20137, Italy
SO Br. J. Pharmacol. (**1990**), 100(4), 831-9
CODEN: BJPCBM; ISSN: 0007-1188
DT Journal
LA English
AB The new compds. phenylethanolaminotetralines (PEAT), unlike the ref. .beta.-adrenoceptor agonists isoprenaline (Iso), ritodrine (Ri) and salbutamol (Sal), produced half-maximal inhibition of spontaneous motility of rat isolated proximal colon at substantially lower concns. (EC50 2.7-30 nM) than those inducing .beta.2-adrenoceptor-mediated responses (relaxation of guinea-pig isolated trachea and rat uterus) and had virtually no chronotropic action (EC50 >3 .times. 10-5 M) on the guinea-pig isolated atrium (a .beta.1-adrenoceptor-mediated response). The nonselective .beta.-adrenoceptor antagonists alprenolol and propranolol prevented the inhibition of rat colon motility by the PEAT with low and different potencies (pA2 values around 7.5 and 6.5 resp.). Conversely alprenolol and propranolol had a higher and similar potency (pA2 values around 9.0) in preventing typical .beta.1- or .beta.2-responses (increase in atrial frequency by Iso or tracheal relaxation by Ri or Sal). The selective .beta.-adrenoceptor antagonists CGP 20712A (.beta.1) and ICI 118,551 (.beta.2) either alone or in combination, did not prevent rat colon motility inhibition by the representative PEAT **SR 58611A**, which was also fully resistant to .alpha.-adrenoceptor, acetylcholine, dopamine, histamine, opioid and 5-hydroxytryptamine antagonists. These results indicate that the PEAT are a new class of .beta.-adrenoceptor agonists and suggest that their preferential intestinal action may be accounted for by selectivity for atypical .beta.-adrenoceptors, abundant in the rat colon and distinct from the currently recognized .beta.1 and .beta.2 subtypes.

IT **107758-36-1**, SR 58375A **107758-39-4**, SR 58373A
107758-41-8, SR 58372 **107758-42-9**, SR 58374
120839-53-4, SR 58572A **121216-30-6**, SR 58590
121216-31-7, SR 58589 **121216-32-8**, SR 58575A
121524-09-2, **SR 58611A** **121524-10-5**,
SR 58612A **121524-11-6**, SR 58613A **129831-97-6**, SR 58825A
RL: BIOL (Biological study)
(as atypical .beta.-adrenergic agonists, in colon)

L99 ANSWER 44 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1989:546279 HCAPLUS
DN 111:146279
TI New developments in .beta.-adrenergic-mediated control of intestinal

motility: gut-specific phenylethanolaminotetralines
AU Manara, Luciano; Bianchetti, Alberto; Croci, Tiziano; Giudice, Antonia
CS Res. Cent., Midy S.p.A., Milan, 20137, Italy
SO Fidia Res. Found. Symp. Ser. (**1989**), 2(Neurochem. Pharmacol.-Tribute B. B. Brodie), 131-47
CODEN: FRFSEL; ISSN: 1040-0451
DT Journal
LA English
GI



I

AB The pharmacol. of the title compds. (I; X = H or Cl; Y = OH or OCH2CO2Et) was studied in lab. animals and in in vitro prepns. These compds. inhibit spontaneous motility of the rat colon in vitro and in vivo through an atypical .beta.-adrenergic mechanism and, unlike ref. .beta.-adrenoceptor agonists, are gut-specific. Structure-activity relations are discussed.
IT **107758-36-1**, SR 58375A **107758-39-4**, SR 58373A
107758-41-8, SR 58372 **107758-42-9**, SR 58374
120839-53-4, SR 58572A **120839-54-5**, SR 58539B
121216-30-6, SR 58590 **121216-31-7**, SR 58589
121216-32-8, SR 58575A **121489-36-9**, SR 58538B
RL: BIOL (Biological study)
(intestinal motility inhibition by, .beta.-adrenergic mechanism in, structure in relation to)

L99 ANSWER 45 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1989:439023 HCAPLUS
DN 111:39023
TI O-alkylation process for N-(hydroxyaralkyl)phenylethanolamines useful as drug intermediates, and the N-protected intermediates thereof
IN Boigegrain, Robert; Cecchi, Roberto; Boveri, Sergio
PA SANOFI, Fr.; Midy S.p.A.
SO Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 303546	A2	19890215	EP 1988-402095	19880811 <--
EP 303546	A3	19901017		
EP 303546	B1	19941228		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
FR 2619379	A1	19890217	FR 1987-11498	19870812 <--
FR 2619379	B1	19900112		
FR 2632637	A1	19891215	FR 1988-7948	19880614 <--
FR 2632637	B1	19901012		
US 4927955	A	19900522	US 1988-230860	19880811 <--
ES 2067483	T3	19950401	ES 1988-402095	19880811 <--
JP 01066152	A2	19890313	JP 1988-202621	19880812 <--
JP 2611816	B2	19970521		
JP 09110811	A2	19970428	JP 1996-145620	19880812 <--
DK 8902938	A	19891215	DK 1989-2938	19890614 <--
DK 172256	B1	19980209		
EP 347313	A2	19891220	EP 1989-401661	19890614 <--

	EP 347313	A3	19901219			
	EP 347313	B1	19931215			
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE					
	JP 02196760	A2	19900803	JP 1989-153580	19890614	<--
	JP 2829306	B2	19981125			
	AT 98628	E	19940115	AT 1989-401661	19890614	<--
	ES 2062062	T3	19941216	ES 1989-401661	19890614	<--
	US 5041606	A	19910820	US 1990-488137	19900305	<--
	US 5159103	A	19921027	US 1992-825841	19920128	<--
	US 5202466	A	19930413	US 1992-922486	19920731	<--
	US 5347037	A	19940913	US 1993-114190	19930901	<--
PRAI	FR 1987-11498		19870812	<--		
	FR 1988-7948		19880614	<--		
	US 1988-230860		19880811	<--		
	JP 1988-202621		19880812	<--		
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OS CASREACT 111:39023; MARPAT 111:39023

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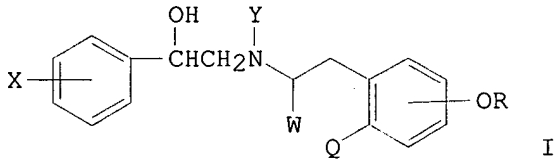

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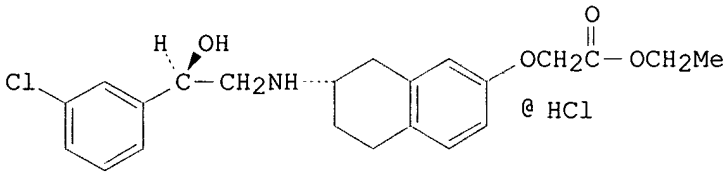

II

AB Title amines I (X = H, halo, CF3, alkyl; W = Me and Q = H; or WQ = CH2CH2; R = Y = H) undergo N-protection at Y, O-alkylation by Hal-CH2CO2R1 (Hal = Cl, Br, iodo; R1 = alkyl), and deblocking at Y to give I (Y = H, R = CH2CO2R1), which show spasmolytic activity. 2-Amino-7-methoxytetralin underwent resoln. by (+)- and (-)-mandelic acids, the latter giving the salt of (-)-amine, and then demethylation by 48% HBr to give (S)-(-)-2-amino-7-hydroxytetralin. This was condensed with (R)-3-chloromandelic acid to give the amide, which was reduced by BH3.SMe2 to give N-[(2S)-7-hydroxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-(3-chlorophenyl)-2-hydroxyethanamine. This compd. underwent quant. N-protection by di-tert-Bu dicarbonate in DMF, and the N-tert-butoxycarbonyl deriv. underwent O-alkylation of 7-OH by BrCH2CO2Et and K2CO3 in refluxing Me2CO, deprotection by CF3CO2H in CH2Cl2, and salification in EtOH to give 22% (ethoxycarbonylmethoxytetrahydronaphthyl)(chlorophenyl)hydroxyethanamine-HCl II. The IC50 of II for inhibition of spontaneous motility of the rat colon in vitro was 3.5 .times. 10-9 M.

IT **120839-53-4P 121216-30-6P 121216-31-7P**
121216-32-8P 121251-85-2P 121312-24-1P
121489-40-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, in prepn. of phenylethanolamine drugs)

IT **120839-54-5P 121489-31-4P 121489-33-6P**

121489-35-8P 121489-36-9P 121489-39-2P
121524-07-0P 121524-08-1P 121524-09-2P
121524-10-5P 121524-11-6P
RL: **BAC (Biological activity or effector, except adverse)**; SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as drug)

L99 ANSWER 46 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1989:423206 HCAPLUS
DN 111:23206
TI Process for the preparation of phenylethanolaminotetralins as drugs
IN Boigegrain, Robert; Cecchi, Roberto; Boveri, Sergio
PA SANOFI, Fr.; Midy S.p.A.
SO Eur. Pat. Appl., 15 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	EP 303545	A2	19890215	EP 1988-402094	19880811	<--
	EP 303545	A3	19890524			
	EP 303545	B1	19920617			
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	FR 2619378	A1	19890217	FR 1987-11497	19870812	<--
	FR 2619378	B1	19891215			
	FR 2629453	A1	19891006	FR 1988-4219	19880330	<--
	FR 2629453	B1	19901005			
	FR 2632636	A1	19891215	FR 1988-7947	19880614	<--
	FR 2632636	B1	19910322			
	AT 77364	E	19920715	AT 1988-402094	19880811	<--
	ES 2045164	T3	19940116	ES 1988-402094	19880811	<--
	JP 01066149	A2	19890313	JP 1988-202622	19880812	<--
	JP 2731913	B2	19980325			
	US 5198586	A	19930330	US 1990-603247	19901025	<--
	US 5235103	A	19930810	US 1992-990762	19921215	<--
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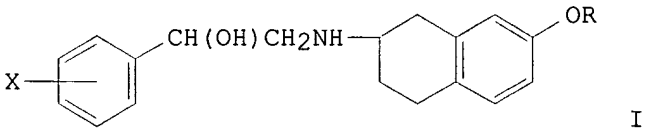
	FR 1988-4219		19880330	<--		
	FR 1988-7947		19880614	<--		
	EP 1988-402094		19880811	<--		
	US 1988-231374		19880811	<--		
	US 1990-603247		19901025	<--		

OS MARPAT 111:23206
GI



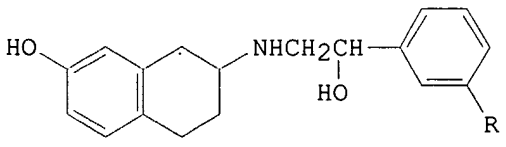
I

AB The title compds. I (X = H, halo, CF3, lower alkyl; R = H, Me group substituted with CO2H, carbalkoxy) and pharmaceutically acceptable salts thereof, useful as drugs (no data), were prepd. Amidation of 3-chloromandelic acid with 2-amino-7-hydroxytetralin, followed by redn. by LiAlH4, gave N-(7-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)-2-(3-chlorophenyl)-2-hydroxyethanamine.
IT **107758-16-7P 107758-23-6P 107758-43-0P**
120839-53-4P 121216-30-6P 121216-31-7P
121216-32-8P 121216-37-3P 121251-85-2P

121312-24-1P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as drug)

L99 ANSWER 47 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1989:225302 HCAPLUS
DN 110:225302
TI Inhibition of rat colonic motility and cardiovascular effects of new gut-specific beta-adrenergic phenylethanolaminotetralines
AU Giudice, Antonina; Croci, Tiziano; Bianchetti, Alberto; Manara, Luciano
CS Res. Cent., MIDY S.p.A., Milan, 20137, Italy
SO Life Sci. (**1989**), 44(19), 1411-17
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
AB The ability of the new putative .beta.-adrenergic agonists, the phenylethanolaminotetralines (PEATs), to inhibit intestinal motility was studied in relation to their cardiovascular effects in anesthetized rats. The representative PEATs SR 58375A, SR 58572A, and SR 58539B and the ref. .beta.-adrenergic agonists isoproterenol, salbutamol, and ritodrine caused dose-related inhibition of proximal colon spontaneous motility: ED50 210, 92, and 19; 5.6, 176, and 201 .mu.g/kg, i.v., resp. This inhibition was prevented by the .beta.-adrenergic antagonist alprenolol, but not by desipramine (which prevented the inhibition of clonic motility by tyramine and enhanced that by norepinephrine). The minimal EDs (MED) of isoproterenol, salbutamol, and ritodrine raising heart rate and (or) lowering blood pressure (by 10-20%), was substantially lower (about 1/10 to 1/150) than their ED50 for inhibition of colonic motility. The MED raising heart rate of the 3 PEATs, on the other hand, was .apprx.2 (SR 58375A and SR 58572A) to 5 (SR 58539B) times their ED50 for inhibition of colonic motility. None of the PEATs lowered blood pressure up to the top tested dose. Therefore the PEATs may prove preferable to the currently best tolerated .beta.-adrenoceptor agonists, because they appear less liable to induce cardiovascular side effects. This supports the prospective therapeutic interest of PEATs for intestinal hypermotility disorders.
IT **107758-36-1 120839-53-4 120839-54-5**
RL: BIOL (Biological study)
(intestine motility decrease by, cardiovascular effect in relation to)

L99 ANSWER 48 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1988:198231 HCAPLUS
DN 108:198231
TI Inhibition of rat colon motility by stimulation of atypical beta-adrenoceptors with new gut-specific agents
AU Croci, Tiziano; Cecchi, Roberto; Tarantino, Antonio; Aureggi, Giulio; Bianchetti, Alberto; Boigegrain, Robert; Manara, Luciano
CS Res. Cent., MIDY S.p.A., Milan, 20137, Italy
SO Pharmacol. Res. Commun. (**1988**), 20(2), 147-51
CODEN: PLRCAT; ISSN: 0031-6989
DT Journal
LA English
GI



@ HCl

I, R=H
II, R=Cl

AB The new putative .beta.-adrenergic agonists SR 58306A (I) and SR 58339A (II) were studied in vitro in comparison with ref. compds. I and II, unlike isoprenaline and the .beta.2-selective adrenergic agonists salbutamol and ritodrine, potently inhibited rat colon spontaneous contractions. They did not increase guinea pig atrium frequency or relax guinea pig trachea. The nonselective .beta.-adrenergic antagonists alprenolol, pindolol, and propranolol competitively antagonized the action of I on the colon, whereas the selective antagonists atenolol (.beta.1-) and ICI 118551 (.beta.2-) did not. In the same prepn. only alprenolol competitively antagonized isoprenaline; the antagonism by either pindolol or propanolol was not competitive. These results suggest that in the rat colon isoprenaline interacts with different .beta.-receptor subclasses, whereas the 2 new gut-specific compds. inhibit colonic motility by selectively stimulating atypical .beta.-adrenoceptors.

IT **107758-16-7 107758-24-7**
RL: BIOL (Biological study)
(intestine motility inhibition by, atypical .beta.-adrenergic receptors in relation to)

L99 ANSWER 49 OF 49 HCAPLUS COPYRIGHT 2002 ACS
AN 1987:156084 HCAPLUS
DN 106:156084
TI Phenylethanolaminotetralins, a process for their preparation, and pharmaceutical compositions containing them
IN Cecchi, Roberto; Boigegrain, Robert; Bianchetti, Alberto; Poggesi, Elena; Croci, Tiziano
PA SANOFI, Fr.; Midy S.p.A.
SO Eur. Pat. Appl., 40 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	EP 211721	A1	19870225		EP 1986-401494	19860704	<--
	EP 211721	B1	19891004				
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE						
	FR 2584712	A1	19870116		FR 1985-10559	19850710	<--
	FR 2584712	B1	19871127				
	FR 2598410	A1	19871113		FR 1986-6626	19860507	<--
	FR 2598410	B1	19880916				
	IL 79323	A1	19900319		IL 1986-79323	19860702	<--
	ES 2002717	A6	19881001		ES 1986-121	19860704	<--
	AT 46900	E	19891015		AT 1986-401494	19860704	<--
	ZA 8605082	A	19870325		ZA 1986-5082	19860708	<--
	CA 1260493	A1	19890926		CA 1986-513357	19860708	<--
	NO 8602773	A	19870112		NO 1986-2773	19860709	<--
	NO 165190	B	19901001				
	NO 165190	C	19910109				
	AU 8659889	A1	19870115		AU 1986-59889	19860709	<--
	AU 596976	B2	19900524				
	FI 8602907	A	19870111		FI 1986-2907	19860710	<--
	FI 85692	B	19920214				
	FI 85692	C	19920525				
	DK 8603285	A	19870111		DK 1986-3285	19860710	<--
	DK 167353	B1	19931018				
	JP 62063549	A2	19870320		JP 1986-163514	19860710	<--
	JP 05071581	B4	19931007				
	US 4707497	A	19871117		US 1986-883961	19860710	<--
PRAI	FR 1985-10559		19850710	<--			
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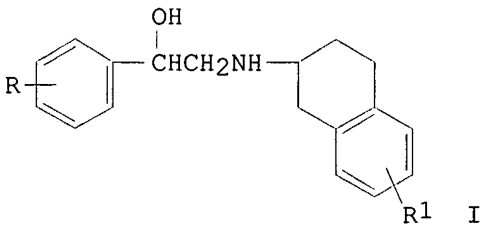
OS CASREACT 106:156084
GI



I

AB The title compds. [I; R = H, halo, alkyl, CF3; R1 = OH, (substituted) alkoxy] and their salts, useful as lipolytic agents, are prepd. A MeOH soln. of 0.8 g 2-amino-1-phenylethanol and 1 g 7-methoxy-2-tetralone was reacted at 35.degree. over 4 h in the presence of H2 and PtO2 to give 37% I.HCl (R = H, R1 = 7-MeO) which (30 mg) was the active ingredient in a sterile parenteral soln. also contg. 5 mg NaCl and 2 mL distd. H2O. The title compds. show strong lipolytic activity both in vitro and in vivo in brown and white adipose tissue.

IT **107758-10-1P 107758-11-2P 107758-12-3P**
107758-13-4P 107758-14-5P 107758-15-6P
107758-16-7P 107758-18-9P 107758-19-0P
107758-20-3P 107758-21-4P 107758-22-5P
107758-23-6P 107758-24-7P 107758-25-8P
107758-26-9P 107758-27-0P 107758-28-1P
107758-29-2P 107758-30-5P 107758-31-6P
107758-32-7P 107758-33-8P 107758-34-9P
107758-35-0P 107758-36-1P 107758-37-2P
107758-38-3P 107758-39-4P 107758-40-7P
107758-41-8P 107758-42-9P 107758-43-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antiobesity agent)

=> fil reg
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DICTIONARY FILE UPDATES: 11 OCT 2002 HIGHEST RN 460983-61-3

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http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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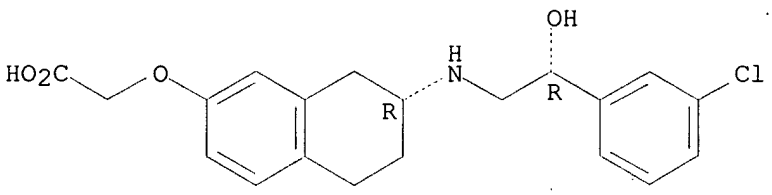
L95 ANSWER 1 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 191533-25-2 REGISTRY
CN Acetic acid, [[(7R)-7-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, [R-(R*,R*)]-
OTHER NAMES:
CN SR 58878
FS STEREOSEARCH
MF C20 H22 Cl N O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



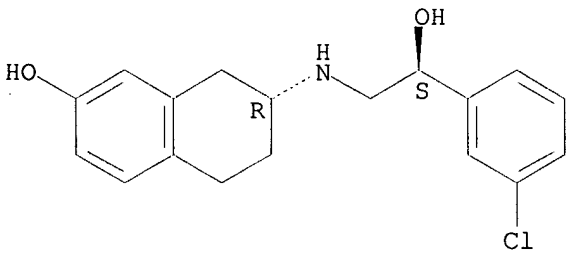
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 127:61038

L95 ANSWER 5 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 158223-17-7 REGISTRY
CN 2-Naphthalenol, 7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-, hydrochloride, [S-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C18 H20 Cl N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS
CRN (121216-30-6)

Absolute stereochemistry.

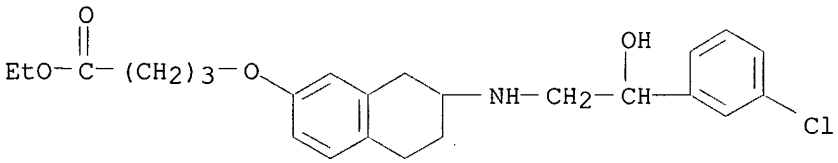


HCl

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 121:230444

L95 ANSWER 10 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 132990-76-2 REGISTRY
CN Butanoic acid, 4-[[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C24 H30 Cl N O4
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

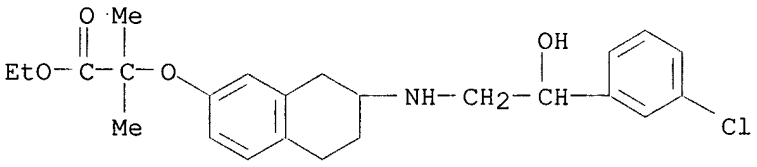


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 114:185045

L95 ANSWER 15 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 132990-67-1 REGISTRY
CN Propanoic acid, 2-[[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-2-methyl-, ethyl ester, hydrochloride (9CI) (CA INDEX NAME)
MF C24 H30 Cl N O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (132990-77-3)



● HCl

2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

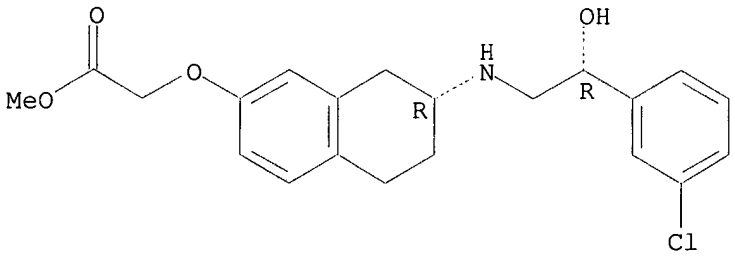
REFERENCE 1: 115:57179

REFERENCE 2: 114:185045

L95 ANSWER 20 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 121489-39-2 REGISTRY
CN Acetic acid, [[7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-

tetrahydro-2-naphthalenyl]oxy]-, methyl ester, hydrochloride, [R-(R*,R*)]-
(9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H24 Cl N O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (121489-31-4)

Absolute stereochemistry.



● HCl

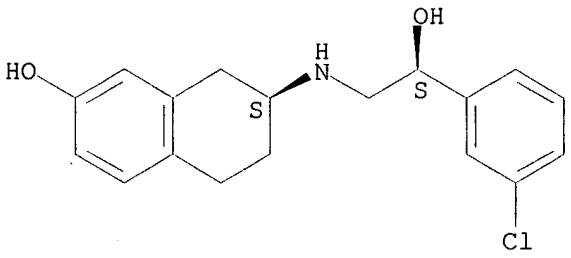
2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 115:57179

REFERENCE 2: 111:39023

L95 ANSWER 25 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 121216-32-8 REGISTRY
CN 2-Naphthalenol, 7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-
tetrahydro-, hydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SR 58575A
FS STEREOSEARCH
DR 121489-41-6
MF C18 H20 Cl N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS, DDFU, DRUGU, USPATFULL

Absolute stereochemistry.



HCl

6 REFERENCES IN FILE CA (1962 TO DATE)
6 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 121:230444

REFERENCE 2: 117:185365

REFERENCE 3: 113:165225

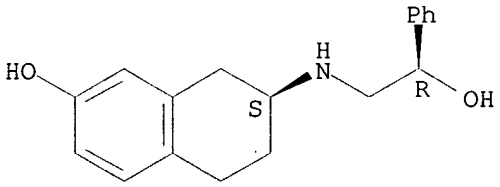
REFERENCE 4: 111:146279

REFERENCE 5: 111:39023

REFERENCE 6: 111:23206

L95 ANSWER 30 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 107758-42-9 REGISTRY
CN 2-Naphthalenol, 5,6,7,8-tetrahydro-7-[(2-hydroxy-2-phenylethyl)amino]-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SR 58374
FS STEREOSEARCH
MF C18 H21 N O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

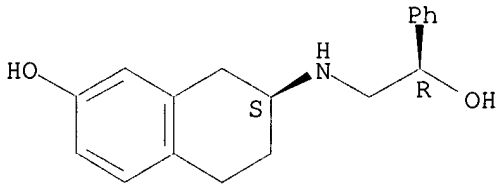
REFERENCE 1: 113:165225

REFERENCE 2: 111:146279

REFERENCE 3: 106:156084

L95 ANSWER 35 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 107758-37-2 REGISTRY
CN 2-Naphthalenol, 5,6,7,8-tetrahydro-7-[(2-hydroxy-2-phenylethyl)amino]-, hydrochloride, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SR 58374A
FS STEREOSEARCH
MF C18 H21 N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (107758-42-9)

Absolute stereochemistry.



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3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

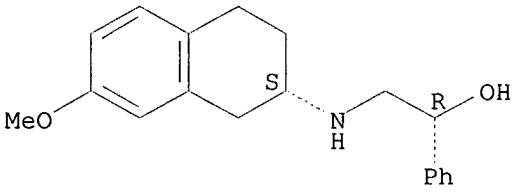
REFERENCE 1: 121:230444

REFERENCE 2: 117:185365

REFERENCE 3: 106:156084

L95 ANSWER 40 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 107758-32-7 REGISTRY
CN Benzenemethanol, .alpha.-[[(1,2,3,4-tetrahydro-7-methoxy-2-naphthalenyl)amino]methyl]-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H23 N O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

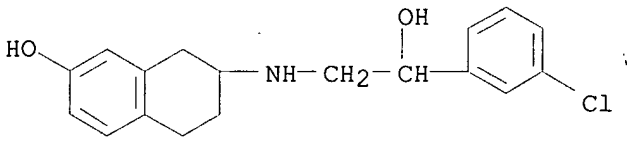
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 106:156084

L95 ANSWER 45 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 107758-26-9 REGISTRY
CN 2-Naphthalenol, 7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-, (2E)-2-butenedioate (salt) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Naphthalenol, 7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-5,6,7,8-tetrahydro-, (E)-2-butenedioate (salt)
FS STEREOSEARCH
MF C18 H20 Cl N O2 . x C4 H4 O4
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

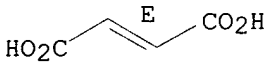
CRN 107758-23-6
CMF C18 H20 Cl N O2



CM 2

CRN 110-17-8
CMF C4 H4 O4

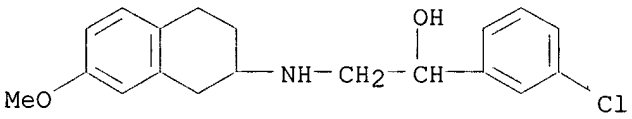
Double bond geometry as shown.



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 106:156084

L95 ANSWER 50 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 107758-21-4 REGISTRY
CN Benzenemethanol, 3-chloro-.alpha.-[[(1,2,3,4-tetrahydro-7-methoxy-2-naphthalenyl)amino]methyl]-, hydrochloride (9CI) (CA INDEX NAME)
MF C19 H22 Cl N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (107758-22-5)



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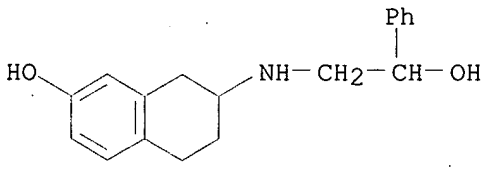
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 106:156084

L95 ANSWER 55 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 107758-16-7 REGISTRY
CN 2-Naphthalenol, 5,6,7,8-tetrahydro-7-[(2-hydroxy-2-phenylethyl)amino]-, hydrochloride (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SR 58306A
MF C18 H21 N O2 . Cl H

SR CA
LC STN Files: ADISINSIGHT, BIOBUSINESS, BIOSIS, CA, CAPLUS, DDFU, DRUGU, MEDLINE, PHAR, PROMT, USPATFULL
CRN (107758-43-0)



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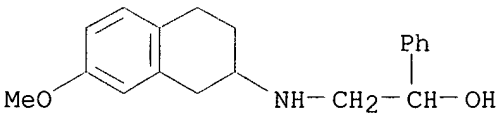
3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 111:23206

REFERENCE 2: 108:198231

REFERENCE 3: 106:156084

L95 ANSWER 60 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 107758-11-2 REGISTRY
CN Benzenemethanol, .alpha.-[[(1,2,3,4-tetrahydro-7-methoxy-2-naphthalenyl)amino]methyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C19 H23 N O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT, USPATFULL

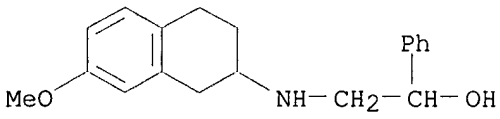


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 106:156084

L95 ANSWER 61 OF 61 REGISTRY COPYRIGHT 2002 ACS
RN 107758-10-1 REGISTRY
CN Benzenemethanol, .alpha.-[[(1,2,3,4-tetrahydro-7-methoxy-2-naphthalenyl)amino]methyl]-, hydrochloride (9CI) (CA INDEX NAME)
MF C19 H23 N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (107758-11-2)



● HCl

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 106:156084

=> fil reg
FILE 'REGISTRY' ENTERED AT 10:42:57 ON 13 OCT 2002
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 11 OCT 2002 HIGHEST RN 460983-61-3
DICTIONARY FILE UPDATES: 11 OCT 2002 HIGHEST RN 460983-61-3

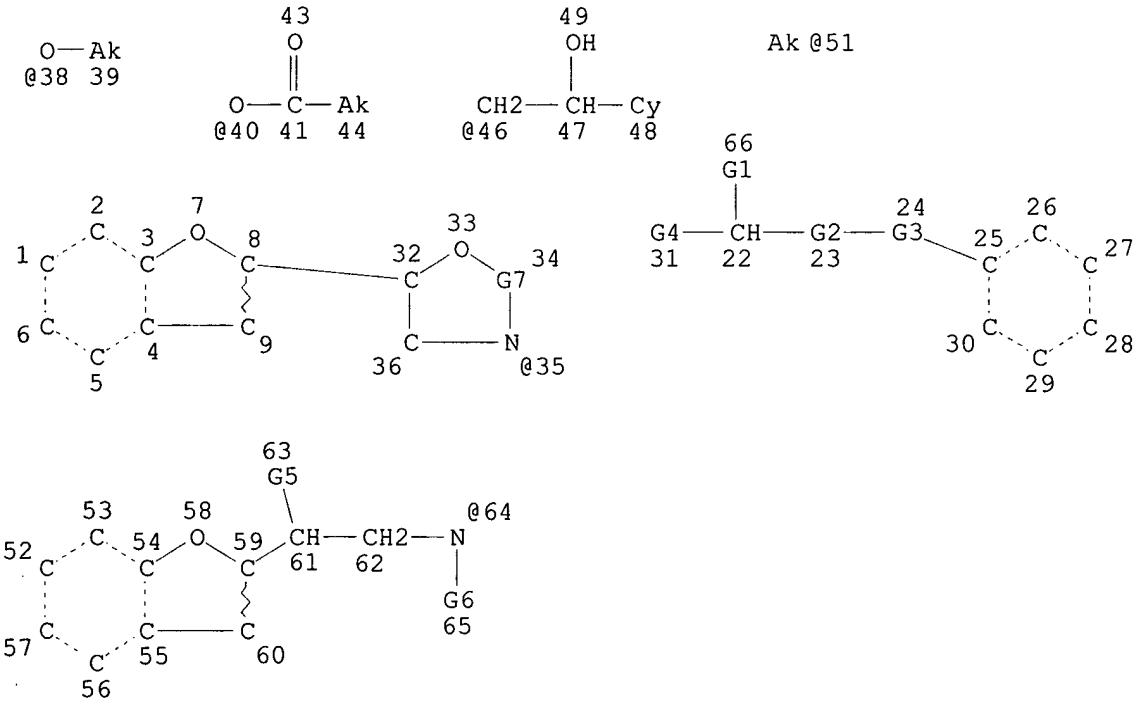
TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sta que l102
L100 STR



VAR G1=H/51
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REP G3=(0-1) O
VAR G4=35/64
VAR G5=OH/38/40
VAR G6=H/46
REP G7=(1-3) C
NODE ATTRIBUTES:
CONNECT IS E1 RC AT 39
CONNECT IS E1 RC AT 44
CONNECT IS E1 RC AT 51
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 32 8 25
NUMBER OF NODES IS 50

STEREO ATTRIBUTES: NONE
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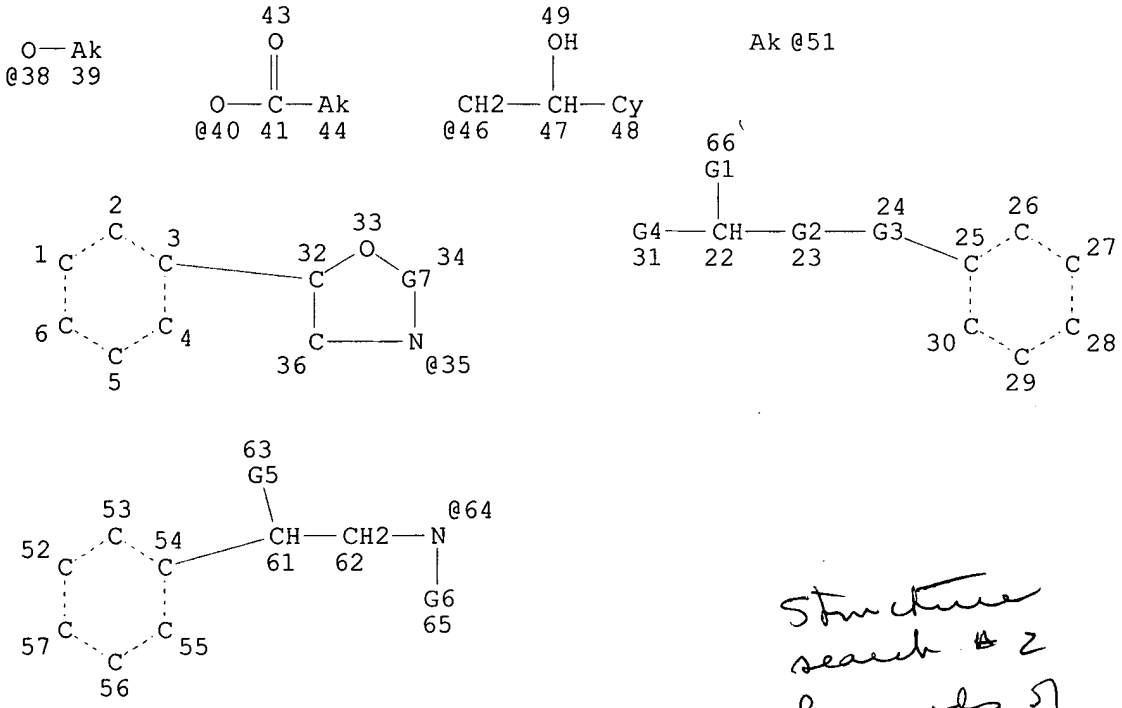
SEARCH TIME: 00.00.02

=> d sta que l105
L103 STR



Structure search # 2 for compds 57 Formula IV

VAR G1=H/51
REP G2=(1-3) CH2
REP G3=(0-1) O
VAR G4=35/64
VAR G5=OH/38/40
VAR G6=H/46
REP G7=(1-3) C
NODE ATTRIBUTES:
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 25 32 3 54
NUMBER OF NODES IS 44

STEREO ATTRIBUTES: NONE
L105 4534 SEA FILE=REGISTRY SSS FUL L103

100.0% PROCESSED 248795 ITERATIONS 4534 ANSWERS
SEARCH TIME: 00.00.11

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L103 STR L100
L104 17 S L103
L105 4534 S L103 FUL
SAV L105 JKIM44531F/A

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L106            STR L103
L107       4607 S L102 OR L105
L108         50 S L106 CSS SAM SUB=L107
L109       2224 S L106 CSS FUL SUB=L107
                SAV L109 JKIM44531G/A
L110          2 S L102 AND L109
L111         73 S L102 NOT L110

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L112         10 S L111
L113         10 S L112 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L114          5 S L113 AND (1 OR 63)/SC,SX
L115          3 S L111 (L) (THU OR BAC)/RL
L116          6 S L114,L115
L117          4 S L112 NOT L116
                SEL DN AN 2
L118          3 S L117 NOT E12-E14
L119          9 S L116,L118

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L120       2222 S L109 NOT L110
L121       2312 S L105 NOT L120

     FILE 'HCAPLUS' ENTERED AT 10:40:08 ON 13 OCT 2002
L122        508 S L120
L123       2818 S L121
L124         78 S L120(L)THU/RL
L125        666 S L121 (L) THU/RL
L126        324 S L122,L123 AND 63/SC
L127        505 S L124-L126 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L128       1213 S BETA 3 (L) ADRENOCEPTOR
L129        886 S BETA 3 (L) ADRENERGIC (L) RECEPTOR
L130         24 S L127 AND L128,L129

     FILE 'REGISTRY' ENTERED AT 10:42:57 ON 13 OCT 2002

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 10:43:18 ON 13 OCT 2002
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FILE COVERS 1907 - 13 Oct 2002  VOL 137 ISS 16
FILE LAST UPDATED: 11 Oct 2002  (20021011/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.
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=> d l130 bib abs hitrn retable tot

L130 ANSWER 1 OF 24  HCAPLUS  COPYRIGHT 2002 ACS
AN   1999:282201  HCAPLUS
DN   130:311793
TI   Preparation of amides as antidiabetics
IN   Maruyama, Tatsuya; Suzuki, Takayuki; Onda, Kenichi; Hayakawa, Masahiko;
     Moritomo, Hiroyuki; Kimizuka, Tetsuya; Matsui, Tetsuo
PA   Yamanouchi Pharmaceutical Co., Ltd., Japan
SO   PCT Int. Appl., 45 pp.
     CODEN: PIXXD2
DT   Patent
LA   Japanese
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.   DATE
     ---------------    ----  --------       ---------------   --------
PI   WO 9920607         A1    19990429       WO 1998-JP4671    19981015 <--
         W:  AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE,
             GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
             LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI,
             SK, SL, TJ, TM, TR, TT, UA, [illegible] AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, [illegible] DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, [illegible] CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, [illegible]
     AU 9889288          A1    19990506       [illegible]       1013 <--
     AU 736676           B2    20010802       [illegible]
     CA 2305802          AA    19990429       [illegible]       1015 <--
     AU 9894621          A1    19990510       [illegible]       1015 <--
     BR 9804500          A     20000411       [illegible]       1015 <--
     EP 1028111          A1    20000816       [illegible]       1015 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI
     JP 3193706          B2    20010730       JP 2000-516949    19981015 <--
     CN 1218045          A     19990602       CN 1998-121375    19981016 <--
     US 6346532          B1    20020212       US 2000-529096    20000407 <--
     NO 2000001983       A     20000414       NO 2000-1983      20000414 <--
PRAI JP 1997-285778      A     19971017  <--
     WO 1998-JP4671      W     19981015
OS   MARPAT 130:311793
GI
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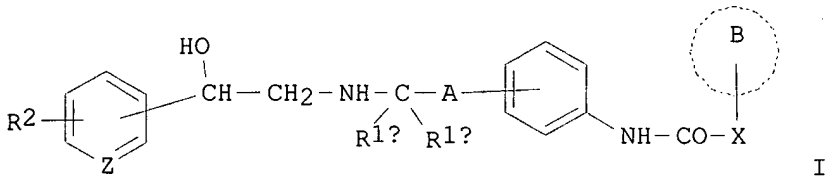
Refs for search #2 — limited to β3 adrenoceptors + date



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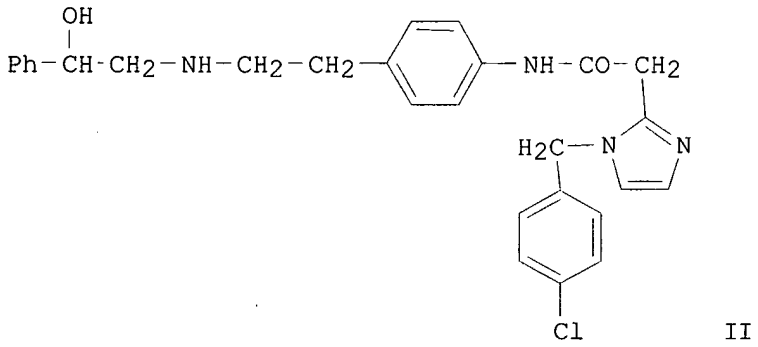

II

AB The title compds. I [ring B = an optionally substituted heteroaryl optionally fused with a benzene ring; X = a bond, lower alkylene or lower alkenylene (optionally substituted by hydroxy or lower alkyl), carbonyl, or NH (further details related to X are given); A = a lower alkylene or a group represented by (lower alkylene)-O; R1a and R1b = hydrogen or lower alkyl; R2 = hydrogen or halogeno; and Z = nitrogen or CH] are prepd. I are useful as diabetes remedies which not only function to accelerate the secretion of insulin and enhance insulin sensitivity but also have an anti-obesity action and an antihyperlipemic action based on their selective stimulative action on .beta.3 receptor. For example, imidazole deriv. II was prepd. Compds. of this invention significantly decreased blood sugar in mice.

IT **223672-09-1P 223672-10-4P 223672-11-5P**
223672-12-6P 223672-13-7P 223672-14-8P
223672-15-9P 223672-16-0P 223672-17-1P
223672-18-2P 223672-19-3P 223672-20-6P
223672-21-7P 223672-22-8P 223672-23-9P
223672-24-0P 223672-25-1P 223672-26-2P
223672-27-3P 223672-29-5P 223672-30-8P
223672-31-9P 223672-32-0P 223672-34-2P
223672-36-4P 223672-38-6P 223672-40-0P
223672-42-2P 223672-44-4P 223672-46-6P
223672-47-7P 223672-48-8P 223672-49-9P
223672-50-2P 223672-51-3P 223672-52-4P
223672-53-5P 223672-55-7P 223672-58-0P
223672-60-4P 223672-63-7P 223672-65-9P
223672-66-0P 223672-67-1P 223672-68-2P
223672-69-3P 223672-70-6P 223672-71-7P
223672-72-8P 223672-73-9P 223672-74-0P
223672-75-1P 223672-76-2P 223672-77-3P
223672-78-4P 223672-79-5P 223672-80-8P
223672-81-9P 223672-82-0P 223672-83-1P
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223672-93-3P 223672-94-4P 223672-95-5P
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223673-65-2P 223673-66-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of amides as antidiabetics)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Merck & Co Inc	1995			JP 07-10827 A	HCAPLUS
Merck & Co Inc	1995			US 5553475 A	
Merck & Co Inc	1995			WO 93/19861 A1	
Merck & Co Inc	1997			JP 09-512275 A	
Merck & Co Inc	1997			US 5541197 A	HCAPLUS
Merck & Co Inc	1997			EP 757674 A1	HCAPLUS
Merck & Co Inc	1997			WO 95/29159 A1	HCAPLUS
Takeda Chem Ind Ltd	1996			JP 08-92228 A	HCAPLUS
Takeda Chem Ind Ltd	1996			US 5614544 A	HCAPLUS
Takeda Chem Ind Ltd	1996			EP 643050 A1	HCAPLUS

L130 ANSWER 2 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:32572 HCAPLUS
DN 130:76508
TI Functional evidence for atypical .beta.-adrenoceptors in human-isolated taenia coli
AU Kelly, J.; Sennitt, M. V.; Stock, M. J.; Arch, J. R. S.
CS SmithKline Beecham Pharmaceuticals, Welwyn, AL6 9AR, UK
SO Pharmacology Reviews and Communications (**1998**), 10(2), 143-152
CODEN: PHRCF6
PB Harwood Academic Publishers
DT Journal
LA English
AB .beta.-**Adrenoceptor** agonists displayed a rank order of potency for relaxation of spontaneous or K-induced tone in human isolated taenia coli of (-)-isoprenaline .gtoreq. noradrenaline > fenoterol = CGP 12177, CGP 12177 being a partial agonist. In the presence of a concn. of CGP 12177 (100 .mu.M) that exerted a max. effect, isoprenaline (100 .mu.M) had no further effect. The rodent .**beta.3-adrenoceptor** agonist BRL-37344 had no effect and isoprenaline elicited a normal response in the presence of BRL-37344 (100 .mu.M). Isoprenaline-induced relaxations of spontaneous and carbachol-induced tone were antagonized by the selective .beta.1-**adrenoceptor** antagonist CGP 20712A (30 nM; apparent pA2 value=8.9) but not by the .beta.2-**adrenoceptor** antagonist ICI 118,551 (30 nM). The .beta.1/.beta.2-**adrenoceptor** antagonist nadolol (1, 10, and 100 .mu.M) antagonized isoprenaline competitively with a pA2 value of only 6.7. This suggests that nadolol blocks the action of isoprenaline at a non-.beta.1/.beta.2-**adrenoceptor** (possibly a .**beta.3-adrenoceptor**), although a component of .beta.1-**adrenoceptor** antagonism may also be involved. Nadolol (1, 10, and 100 .mu.M) failed to produce any consistent shift of the concn.-response curve to CGP 12177, again suggesting the involvement of

non-.beta.1/.beta.2-**adrenoceptors**, although the lack of any antagonism by 100 .mu.M nadolol questions the role of .**beta.3-adrenoceptors**. These results indicate a role for not only .beta.1- but also .**beta.3** and/or so-called putative ".beta.4"-**adrenoceptors** in human taenia coli.

IT **13392-18-2**, Fenoterol
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(selective .beta.-adrenoceptor agonists reaction in human taenia coli relaxation)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Ahlquist, R	1948	153	586	American Journal of	HCAPLUS
Arch, J	1996	20	191	International Journa	HCAPLUS
Arch, J	1993	13	663	Medical Research Rev	HCAPLUS
Arch, J	1984	309	163	Nature	HCAPLUS
Arch, J	1997	9	141	Pharmacology Reviews	HCAPLUS
Arunlakshana, O	1959	14	48	British Journal of P	HCAPLUS
Berkowitz, D	1995	289	223	European Journal of	HCAPLUS
Bianchetti, A	1990	100	831	British Journal of P	HCAPLUS
Blin, N	1993	44	1094	Journal of Pharmacol	HCAPLUS
Blum-Kaelin, D	1991		315	Adrenoceptors Struct	HCAPLUS
Bond, R	1988	95	723	British Journal of P	HCAPLUS
Bucknell, A	1964	23	164	British Journal of P	MEDLINE
De Ponti, F	1996	117	1374	British Journal of P	HCAPLUS
Dreyer, A	1980	27	2087	Life Sciences	HCAPLUS
Furchgott, R	1972		283	Handbook of Experime	HCAPLUS
Gauthier, C	1996	98	556	Journal of Clinical	HCAPLUS
Gillespie, J	1977	267	767	Journal of Physiolog	MEDLINE
Hedges, A	1971	41	426P	British Journal of P	HCAPLUS
Hoey, A	1996	119	564	British Journal of P	HCAPLUS
Kaumann, A	1996	118	2085	British Journal of P	HCAPLUS
Kaumann, A	1996	117	93	British Journal of P	HCAPLUS
Kaumann, A	1997	18	70	Trends in Pharmacolo	HCAPLUS
Kelly, J	1996	120	207P	British Journal of P	
Kelly, J	1996	16	205	Journal of Autonomic	HCAPLUS
Kirkham, D	1992	105	231P	British Journal of P	
Krief, S	1993	91	344	Journal of Clinical	HCAPLUS
Landi, M	1993	53	344	Life Sciences	
Lands, A	1967	214	597	Nature	HCAPLUS
Lemoine, H	1991	344	56	Naunyn-Schmiedeberg'	HCAPLUS
Levy, B	1959	127	150	Journal of Pharmacol	HCAPLUS
Maggi, C	1997	18	351	Trends in Pharmacolo	HCAPLUS
Manara, L	1995	9	332	Fundamentals of Clin	HCAPLUS
McLaughlin, D	1991	104	152P	British Journal of P	
Middlemiss, D	1986	120	51	European Journal of	HCAPLUS
Molenaar, P	1997	24	647	Clinical and Experim	HCAPLUS
Oriowo, M	1996	7	229	Pharmacology Communi	HCAPLUS
Pak, M	1996	16	1	Journal Of Receptor	HCAPLUS
Roberts, S	1997	120	1527	British Journal of P	HCAPLUS
Sennitt, M	1998	285	1084	J Pharmacol Exp Ther	HCAPLUS
Sugasawa, T	1997	272	21244	Journal of Biologica	HCAPLUS
Wilson, C	1984	100	309	European Journal of	HCAPLUS
Wilson, S	1996	279	214	Journal of Pharmacol	HCAPLUS

L130 ANSWER 3 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:784989 HCAPLUS
DN 130:134103
TI The effects of the .**beta.3-adrenoceptor** agonist BRL 35135 on UCP isoform mRNA expression

AU Emilsson, Valur; Summers, Roger J.; Hamilton, Stephanie; Liu, Yong-Ling; Cawthorne, Michael A.
CS Clore Laboratory, University of Buckingham, Buckingham, MK18 1EG, UK
SO Biochemical and Biophysical Research Communications (**1998**), 252(2), 450-454
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
AB The mitochondrial uncoupling protein UCP-1 uncouples respiration from ATP synthesis in brown adipose tissue (BAT) and thus energy is dissipated as heat. Recently two further isoforms have been identified which may play a similar role in other tissues. We have detd. the effects of the rodent-selective **.beta.3-adrenoceptor** (. **beta.3**-AR) agonist BRL 35135, on **.beta.3**-AR and UCP mRNA levels in tissues from lean and obese (fa/fa) Zucker rats. **.beta.3**-AR mRNA levels were reduced in fa/fa white (WAT) and brown (BAT) adipose tissue relative to levels in lean littermates. BRL 35135 treatment increased expression levels of . **beta.3**-AR mRNA in both genotypes. UCP-2 and UCP-3 mRNA levels in BAT, WAT and skeletal muscle were reduced by 2-3 fold in the fa/fa rats relative to the lean rats. We confirm that BRL 35135 increases BAT UCP-1 mRNA in lean rats, and find that BAT UCP-3 mRNA was reduced 3.2 fold, with no changes in UCP-2 expression. In WAT BRL 35135 increased UCP-2 and UCP-3 expression 2-3 fold in both lean and fa/fa rats. In lean rats, skeletal muscle UCP-3 mRNA was increased 2.3 fold by BRL 35135 whereas UCP-2 was reduced by 2.2 fold. BRL 35135 had no effects on UCP-2 and UCP-3 expression in skeletal muscle of the fa/fa rats. Our results demonstrate that mechanisms regulating UCP isoform synthesis in fa/fa rats are impaired and that WAT could be involved in the thermogenic response of BRL 35135. (c) 1998 Academic Press.
IT **86615-96-5**, BRL 35135
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**.beta.3-adrenoceptor** agonist BRL 35135 effect on UCP isoform mRNA expression)

RETABLE

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Arch, J	1993	13	663	Med Res Rev	HCAPLUS
Arch, J	1984	309	163	Nature	HCAPLUS
Boss, O	1997	408	39	FEBS Lett	HCAPLUS
Boss, O	1996	20	68	Int J Obesity	
Boss, O	1998	273	5	J Biol Chem	HCAPLUS
Brooks, S	1980	286	274	Nature	HCAPLUS
Cawthorne, M	1992	55	252S	Am J Clin Nutr	HCAPLUS
Chomczynski, P	1987	162	156	Anal Biochem	HCAPLUS
Cusin, I	1998	47	1014	Diabetes	HCAPLUS
Dukas, K	1993	215	66	Anal Biochem	HCAPLUS
Emorine, L	1989	245	1118	Science	HCAPLUS
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Evans, B	1996	117	210	Brit J Pharmacol	HCAPLUS
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Jacobsson, A	1985	260	16250	J Biol Chem	HCAPLUS
Krook, A	1998	47	1528	Diabetes	HCAPLUS
Liu, Q	1998	207	1	Gene	HCAPLUS

Liu, Y	1995	114	880	Brit J Pharmacol	
Liu, Y	1996	117	1355	Brit J Pharmacol	HCAPLUS
Matsuda, J	1997	418	200	FEBS Lett	HCAPLUS
Millet, L	1997	100	2665	J Clin Invest	HCAPLUS
Nagase, L	1996	97	2898	J Clin Invest	
Oberkofler, H	1997	38	2125	J Lipid Res	HCAPLUS
Revelli, J	1997	100	1098	J Clin Invest	HCAPLUS
Rothwell, N	1981	389	237	Pflugers Arch	HCAPLUS
Savontaus, E	1998	246	899	Biochem Biophys Res	HCAPLUS
Silva, J	1997	136	251	Eur J Endocrinol	HCAPLUS
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Thurlby, P	1986	64	1111	Can J Physiol Pharma	HCAPLUS
Trayhurn, P	1996	228	605	Biochem Biophys Res	HCAPLUS
Vidal-Puig, A	1997	235	79	Biochem Biophys Res	HCAPLUS
Weigle, D	1998	47	298	Diabetes	HCAPLUS
Wilson, C	1984	4	309	Eur J Pharmacol	

L130 ANSWER 4 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:535771 HCAPLUS
DN 129:198012
TI Preparation of phenethanol derivatives and their use as antidiabetic agents
IN Maruyama, Tatsuya; Onta, Kenichi; Hayakawa, Akihiko; Matsui, Tetsuo
PA Yamanouchi Pharmaceutical Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 20 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 10218861	A2	19980818	JP 1997-21870	19970204 <--

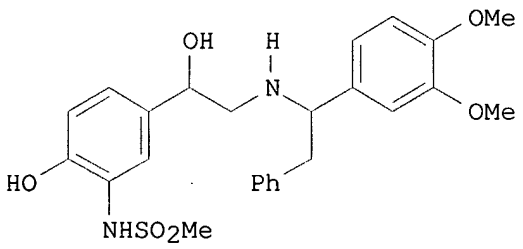
OS MARPAT 129:198012
GI For diagram(s), see printed CA Issue.
AB The derivs. I [ring B = II, III, IV; X, Y = O, S, NR6; R1 = H, lower alkyl; R2 = H, lower alkyl, NHSO2Me, NHCOR3; R3 = H, lower alkyl, mono- or di(lower alkylamino), aryl, aralkyl; R4, R5 = H, lower alkyl, amino; R6 = H, lower alkyl, aralkyl] or their salts as **.beta.3-adrenoceptor** agonists are prepd. Antidiabetic agents contg. I or thir salts as active ingredients are also claimed. I decreased blood glucose of obese and hyperglycemic kk mice with insulin resistance upon both oral and percutaneous administrations. I also increased insulin secretion in normal rats. Prepn. of some of I was given.
IT **211636-04-3P 211636-05-4P 211636-06-5P**
211636-07-6P 211636-08-7P 211636-09-8P
211636-10-1P 211636-11-2P 211636-13-4P
211636-17-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of antidiabetic phenethanol derivs. as **.beta.3-adrenoceptor** agonists)

L130 ANSWER 5 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:471470 HCAPLUS
DN 129:108907
TI Preparation of N-[3-(2-aralkylamino-1-hydroxyethyl)phenyl]methanesulfonamides and analogs as **.beta.3 adrenoceptor** agonists
IN Washburn, William N.; Girotra, Ravindar N.; Sher, Philip M.; Mikkilineni, Amarendra B.; Poss, Kathleen M.; Mathur, Arvind; Bisacchi, Gregory S.; Gavai, Ashvinikumar V.
PA Bristol-Myers Squibb Co., USA

SO U.S., 79 pp., Cont.-in-part of U. S. Ser. No. 171,285, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	US 5776983	A	19980707		US 1994-346543	19941202	<--
	TW 424082	B	20010301		TW 1994-83111890	19941219	<--
	HU 72302	A2	19960429		HU 1994-3694	19941220	<--
	HU 220063	B	20011028				
	CA 2138675	AA	19950622		CA 1994-2138675	19941221	<--
	FI 9406003	A	19950622		FI 1994-6003	19941221	<--
	NO 9404969	A	19950622		NO 1994-4969	19941221	<--
	AU 9481635	A1	19950629		AU 1994-81635	19941221	<--
	AU 688417	B2	19980312				
	JP 07206806	A2	19950808		JP 1994-336251	19941221	<--
	CN 1109050	A	19950927		CN 1994-113297	19941221	<--
	ZA 9410213	A	19960621		ZA 1994-10213	19941221	<--
PRAI	US 1993-171285	B2	19931221	<--			

OS MARPAT 129:108907
GI



I

AB R1SO2NHZ1CH(OH)CHR6NHCR3R4Z2R2 [R1 = alkyl or aryl(alkyl); R2 = (un)substituted Ph; R3 = H, alkyl, heterocyclyl, etc.; R4 = H, alkyl, etc.; R6 = H or alkyl; Z1 = (un)substituted 1,3-phenylene; Z2 = bond, (acyl)methylene, (CH2)2-3] were prepd. as **.beta.3 adrenoceptor** agonists (no data). Thus, 3,4-(MeO)2C6H3CH(NH2)CH2Ph was N-alkylated by 4,3-(PhCH2O)(MeSO2NH)C6H3COCH2Br (prepn. each given) to give, after hydrogenation, title compd. I.

IT **170685-57-1P 170685-58-2P 170685-59-3P**
170685-60-6P 170685-61-7P 170685-62-8P
170685-63-9P 170685-64-0P 170685-65-1P
170685-66-2P 170685-67-3P 170685-68-4P
170685-69-5P 170685-75-3P 170685-78-6P
170685-80-0P 170685-82-2P 170685-83-3P
170685-84-4P 170685-85-5P 170685-86-6P
170685-87-7P 170685-88-8P 170685-89-9P
170685-93-5P 170685-97-9P 170685-98-0P
170686-01-8P 170686-02-9P 170686-03-0P
170686-04-1P 170686-05-2P 170686-06-3P
170686-07-4P 170686-08-5P 170686-09-6P
170686-10-9P 170686-11-0P 170686-13-2P
170686-14-3P 170686-15-4P 170686-16-5P
170686-17-6P 170686-24-5P 170686-25-6P
170686-30-3P 170686-33-6P 170686-34-7P
170686-35-8P 170686-36-9P 170686-37-0P
170686-38-1P 170686-39-2P 170686-40-5P
170686-41-6P 170686-42-7P 170686-43-8P
170686-44-9P 170686-45-0P 170686-46-1P

170686-47-2P 170686-58-5P 170686-59-6P
170686-60-9P 170686-62-1P 170686-63-2P
170686-64-3P 170686-65-4P 170686-66-5P
170686-67-6P 170686-68-7P 170686-69-8P
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170687-60-2P 170687-61-3P 170687-62-4P
170687-63-5P 170687-64-6P 170687-65-7P
170687-66-8P 170687-67-9P 209914-79-4P
209914-83-0P 209914-84-1P 209914-86-3P
209914-87-4P 209914-89-6P 209914-91-0P
209914-92-1P 209914-94-3P 209914-95-4P
209914-97-6P 209914-98-7P 209915-09-3P
209915-16-2P 209915-17-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-[3-(2-aralkylamino-1-hydroxyethyl)phenyl]methanesulfonamides and analogs as **.beta.3 adrenoceptor** agonists)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
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Anon	1965			GB 1005025	
Anon	1971			DE 2048555	HCAPLUS
Anon	1974			GB 1367678	HCAPLUS
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Anon	1975			JP 51143678	HCAPLUS
Anon	1975			JP 51149282	HCAPLUS
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Gould	1971			US 3574741	
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Larsen	1967			US 3341584	
Larsen	1972			US 3660487	HCAPLUS
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Lunts	1972			US 3705233	HCAPLUS
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Lunts	1977			US 4012444	HCAPLUS
Lunts	1978			US 4066755	
Sugihara	1977			US 4035512	

L130 ANSWER 6 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:356059 HCAPLUS
DN 129:90214
TI Differential regulation of uncoupling proteins by chronic treatments with .beta.3-adrenergic agonist BRL 35135 and metformin in obese fa/fa Zucker rat
AU Savontaus, Eriika; Rouru, Juha; Boss, Olivier; Huupponen, Risto; Koulu, Markku
CS Department of Pharmacology, University of Turku, Turku, Finland
SO Biochemical and Biophysical Research Communications (**1998**), 246(3), 899-904
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
AB The expressions of uncoupling proteins 2 and 3 (UCP2; UCP3) mRNA were studied in obese (fa/fa) Zucker rats treated with two wt. gain reducing agents for three weeks. The specific **.beta.3-adrenoceptor** agonist BRL 35135 (0.5 mg/kg/day orally) increased the expression of UCP3 mRNA by 3.8-fold ($P < 0.0001$; two-way ANOVA) and that of UCP1 mRNA by 2.6-fold ($P = 0.014$) in brown adipose tissue, but had no effect on expression of UCP3 mRNA in white fat or in the soleus muscle, or on UCP2 mRNA expression in brown or white fat. The antihyperglycemic metformin (300 mg(kg/day orally) had no effect on expressions of UCP1, UCP2 or UCP3 in any tissue studied. Concns. of plasma insulin were significantly correlated with the levels of white fat UCP2 mRNA (in the control group: $r = 0.89$, $P = 0.0015$) and UCP3 mRNA (in the control group: $r = 0.80$, $P = 0.009$) suggesting that insulin may play a role in the control of UCP2 and UCP3 mRNA expressions in white adipose tissue.
IT **86615-96-5**, BRL 35135
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(.beta.3-adrenergic agonist BRL 35135 and metformin effects on uncoupling proteins 2 and 3)

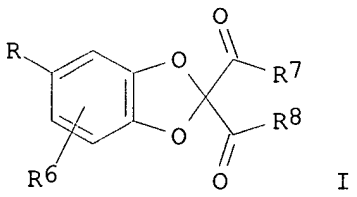
L130 ANSWER 7 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:752946 HCAPLUS
DN 128:34758
TI Preparation of 1, 3-benzodioxole-2,2,-dicarboxylates as **.beta.3-adrenoceptor** agonists
IN Gilbert, Adam Matthew; Grosu, George Theodore; Malamas, Michael Sotirios; Sum, Fuk Wah; Venkatesan, Aranapakam Mudumbai; Francisco, Gerardo De La Cruz
PA American Home Products Corporation, USA
SO PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9743273	A1	19971120	WO 1997-US8148	19970505	<--
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
	CA 2254120	AA	19971120	CA 1997-2254120	19970505	<--
	AU 9730067	A1	19971205	AU 1997-30067	19970505	<--
	AU 730659	B2	20010308			
	EP 901484	A1	19990317	EP 1997-924720	19970505	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO					
	BR 9708948	A	19990803	BR 1997-8948	19970509	<--
	JP 2000510150	T2	20000808	JP 1997-541097	19970509	<--
	KR 2000011001	A	20000225	KR 1998-709151	19981113	<--
PRAI	US 1996-645970	A	19960514	<--		
	WO 1997-US8148	W	19970505	<--		

OS MARPAT 128:34758

GI



I

AB Title compds. [I; R = R1CH(OR2)CH2NR3CR4R5CH2; R1 = (un)substituted Ph; R2 = H or trialkylsilyl; R3 = H or alkoxycarbonyl; R2R3 = CH2, alkylidene, arylmethylene; R4,R5 = H or allyl; R6 = H, halo, alkyl, alkoxy, etc.; R7,R8 = OR9, NR10R11; R9 = H, alkyl, aryl(alkyl), etc.; R10,R11 = H, alkyl, aryl(alkyl), etc.] were prepd. Thus, I [R = 3-ClC6H4CH(OH)CH2NHCHMeCH2, R6 = H](II; R7 = R8 = OH) was esterified by MeOCH2CH2OH to give II (R7 = R8 = OCH2CH2OMe). Data for biol. activity of I were given.

IT **199669-72-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 1, 3-benzodioxole-2,2-dicarboxylates as **.beta. 3-adrenoceptor** agonists)

L130 ANSWER 8 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:482928 HCAPLUS
DN 127:199880
TI Chronic treatment with BRL 35135 potentiates the action of insulin on lipid metabolism
AU Virtanen, Kirsi A.; Rouru, Juha; Haenninen, Virve; Savontaus, Eriika; Rouvari, Taina; Teirmaa, Tomi; Koulu, Markku; Huupponen, Risto
CS Department of Pharmacology and Clinical Pharmacology, University of Turku, Kiinanmyllynkatu 10, Turku, FIN-20520, Finland
SO European Journal of Pharmacology (**1997**), 332(2), 215-218
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier

DT Journal
LA English
AB The effects of a **.beta.3-adrenoceptor** agonist on insulin-induced changes in lipid metab. were studied in obese male Zucker (fa/fa) rats during euglycemic clamp. Rats were treated with BRL 35135 (R,R-(.+-.)-methyl-4-[2-[2-hydroxy-2-(3-chlorophenyl)-ethyl-amino]-propyl]-phenoxyacetate hydrobromide) (0.5 mg/kg per day in drinking water) for three weeks before an euglycemic hyperinsulinemic clamp was performed. Insulin infusion lowered serum non-esterified fatty acids and plasma glycerol more efficiently in BRL 35135-treated than in control rats although plasma insulin remained significantly lower in the BRL 35135-treated than in the control rats during the clamp. In conclusion, chronic treatment with BRL 35135 potentiates the effect of insulin on lipid metab.
IT **86615-96-5**, BRL 35135
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(chronic treatment with **.beta.3-adrenoceptor** agonist BRL 35135 potentiates insulin action on lipid metab.)

L130 ANSWER 9 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:725349 HCAPLUS
DN 126:26853
TI Treatment of glaucoma and ocular hypertension with .beta.3-adrenergic agonists
IN Brazzell, Romulus K.; Dubnick, Bernard
PA American Cyanamid Company, USA
SO U.S., 7 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5578638	A	19961126	US 1993-148154	19931105 <--
	ZA 9408742	A	19950710	ZA 1994-8742	19941104 <--
PRAI	US 1993-148154		19931105 <--		

AB This invention relates to a method of treating glaucoma or reducing intraocular pressure in a patient in need of such treatment which is based on the topical administration to the eye of a mammal or the systemic administration of .beta.2-adrenergic agonists such as di-Na (R,R)-7-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]-7,8-dihydro-6H-indeno[4,3-d]-1,3-dioxole-2,2-dicarboxylate.
IT **127299-93-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(glaucoma and ocular hypertension treatment with .beta.3-adrenergic agonists)

L130 ANSWER 10 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:688208 HCAPLUS
DN 126:26629
TI Rapid inhibition of ob gene expression and circulating leptin levels in lean mice by the **.beta.3-adrenoceptor** agonists BRL 35135A and ZD2079
AU Trayhurn, Paul; Duncan, Jacqueline S.; Rayner, D. V.; Hardie, Laura J.
CS Division Biochemical Sciences, Rowett Research Institute, Bucksburn, Aberdeen, AB21 9SB, UK
SO Biochemical and Biophysical Research Communications (**1996**), 228(2), 605-610

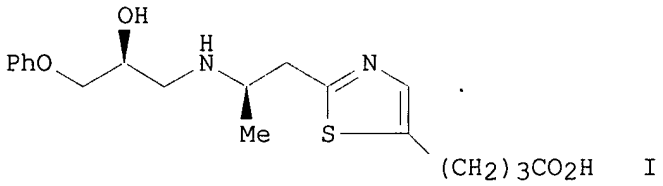
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic
DT Journal
LA English
AB The acute effect of two selective .**beta.3-adrenoceptor** agonists, BRL 35135A and ZD2079, on the expression of the ob gene and plasma leptin levels has been examd. in mice. By 4-5 h after the administration of either .**beta.3**-agonist to lean animals there was a major loss of ob mRNA from epididymal white adipose tissue. This was accompanied by a substantial fall in circulating leptin levels, as measured by an ELISA. Even 24 h after the first administration of .**beta.3**-agonists, ob mRNA levels and circulating leptin levels remained low. In contrast to lean animals, treatment with BRL 35135A had only a minor effect on ob mRNA levels in obese (ob/ob) mice. Regulation of leptin prodn. appears to involve a neg. feedback loop to white adipose tissue through the sympathetic nervous system suppressing ob gene transcription via .**beta.3-adrenoceptors**; an impairment in this loop is evident in the ob/ob mutant.
IT **86615-41-0**, BRL 35135A **178600-17-4**, ZD2079
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(.**beta.3-adrenoceptor** agonists BRL 35135A and ZD2079 inhibition of ob gene expression and leptin level in lean vs. obese mice)

L130 ANSWER 11 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:671324 HCAPLUS
DN 125:317095
TI Improvement of metabolic disorders and visceral fat obesity by the . **beta.3-adrenoceptor** agonist (R*,R*)-(+)-methyl-4-[2-[2-hydroxy-2-(3-chlorophenyl)ethylamino]propyl]-phenoxyacetate hydrobromide (BRL35135A) in genetically obese rodents
AU Hashimoto, Koji; Nagao, Yuji; Ida, Keiichi; Takeda, Mitsuhiro; Murakami, Nobuya; Kato, Katsuaki; Mizota, Masahiro
CS Department of Pharmacology, Mochica Pharmaceutical Co., Ltd., Tokyo, 115, Japan
SO Biochemical Pharmacology (**1996**), 52(10), 1529-1535
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier
DT Journal
LA English
AB The effects of BRL35135A ((R*,R*)-(+)-methyl-4-[2-[2-hydroxy-2-(3-chlorophenyl)ethylamino]propyl]-phenoxyacetate hydrobromide), a . **beta.3-adrenoceptor** agonist, on visceral and s.c. fat wt. and metabolic disorders were studied in genetically obese C57BL/KsJ db/db mice and Zucker fa/fa rats. In db/db mice, four weeks of oral administration of BRL35135A (0.5 and 5 mg/kg/day) decreased body wt. gain and reduced white fat wt. The rates of redn. of white fat wt. were in the order mesenteric fat > retroperitoneal fat > s.c. fat. In fa/fa rats, daily administration of BRL35135A (0.05 mg/kg/day) for 6 wk reduced the visceral white fat wt./total energy intake ratio, particularly for mesenteric fat, without any clear effect on body wt. gain. This tendency of the compd. to exert effects on visceral fat was consistent with the findings that the effect of BRL37344 ((R*,R*)-(+)-methyl-4-[2[2-hydroxy-2-(3-chlorophenyl)ethylamino]propyl]-phenoxyacetic acid), an active metabolite of BRL35135A, on the lipolytic activity of isolated adipocytes and the tissue concn. of [14C]BRL37344 in male Wistar rats were each greater in visceral fat than in s.c. fat. Moreover, BRL35135A at 0.05 mg/kg/day elevated serum insulin levels and improved hyperglycemia in db/db mice without reducing body wt. gain, whereas at doses of 0.5 and 5 mg/kg/day it ameliorated hyperglycemia and hyperlipidemia, and tended to

decrease serum insulin levels. In fa/fa rats, BRL35135A (0.005 mg/kg/day) was also effective in improving hyperinsulinemia, glucose intolerance, and hypertriglyceridemia without any effect on body wt. gain or fat distribution. These findings suggest that the improvement of metabolic disorders by BRL35135A may be due to improvement in insulin resistance as well as redn. of visceral fat wt.

IT **86615-41-0**, BRL35135A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(improvement of metabolic disorders and visceral fat obesity by **.beta.3-adrenoceptor** agonist BRL35135A in genetically obese rodents)

L130 ANSWER 12 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:628808 HCAPLUS
DN 125:316209
TI BMS-187257, a potent, selective, and novel heterocyclic **.beta.3 adrenergic receptor** agonist
AU Fisher, Liesl G.; Sher, Philip M.; Skwish, Stephen; Michel, Inge M.; Seiler, Steven M.; Dickinson, Kenneth E. J.
CS Bristol-Myers Squibb Pharmaceutical Institute, Princeton, NJ, 08543-4000, USA
SO Bioorganic & Medicinal Chemistry Letters (**1996**), 6(19), 2253-2258
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier
DT Journal
LA English
GI



I

AB Novel heterocyclic **.beta.3 adrenergic receptor** agonists were prepd. and evaluated for their ability to bind to human .beta.1, .beta.2, and **.beta.3 adrenergic receptors**. Stimulatory effects on the **.beta.3 adrenergic receptor** were also measured. The 2,5-disubstituted thiazole BMS-187257 (I) was found to be a potent and selective **.beta.3** agonist.

IT **90730-96-4P**, BRL37344
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arylalkanolamine thiazoles as selective **.beta.3 adrenergic receptor** agonist)

L130 ANSWER 13 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:616601 HCAPLUS
DN 125:275666
TI Preparation of pyridyl-substituted sulfonamides as selective **.beta**

.3 adrenergic receptor agonists for the treatment of type II diabetes and obesity

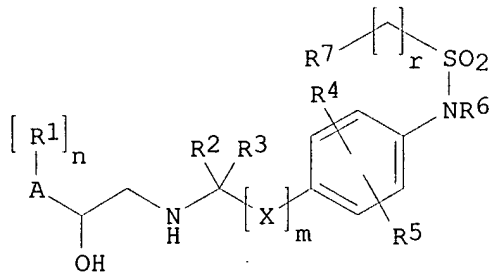
IN Fisher, Michael H.; Naylor, Elizabeth M.; Ok, Dong; Weber, Ann E.; Shih, Thomas; Ok, Hyun
PA Merck and Co., Inc., USA

SO U.S., 35 pp., Cont.-in-part of U. S. Ser. No. 404,565, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 4

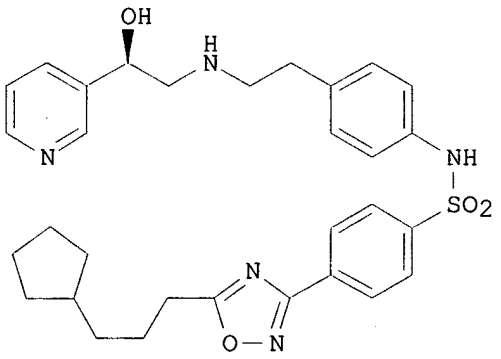
PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI US 5561142	A	19961001		US 1995-445630	19950522	<--
US 5705515	A	19980106		US 1996-684901	19960725	<--
PRAI US 1994-233166	B2	19940426	<--			
US 1995-404565	B2	19950321	<--			
US 1995-445630	A2	19950522	<--			

OS MARPAT 125:275666

GI



I



II

AB The title compds. [I; A = pyridinyl; R1 = OH, O, halo, etc.; R2, R3 = H, C1-10 alkyl, C1-10 alkoxy, etc.; X = CH2, (CH2)2, CH:CH, CH2O; R4, R5 = H, C1-10 alkyl, halo, etc.; R6 =.H, C1-10 alkyl; R7 = (substituted) Ph, naphthyl, a 5- or 6-membered heterocyclic ring, etc.; n = 0-5; m = 0-1; r = 0-3], selective **.beta.3 adrenergic receptor** agonists and therefore useful in the treatment of type II diabetes and obesity as well as neurogenic inflammation, depression, gastrointestinal disorders, gut motility and as lowering triglyceride and cholesterol levels agents, were prepd. by coupling an aminoalkylphenylsulfonamide with an appropriately substituted epoxide. Thus, refluxing (R)-(pyrid-3-yl)oxirane with N-[4-(2-aminoethyl)phenyl]-4-[5-(3-cyclopentylpropyl)[1,2,4]-oxadiazol-3-yl]benzenesulfonamide in dry MeOH afforded the desired product (R)-II. Compds. I were effective at 0.07-350 mg/day when treating diabetes mellitus and/or hyperglycemia.

IT **173902-22-2P 173902-24-4P 173902-26-6P**
173902-30-2P 173902-31-3P 173902-32-4P
173902-33-5P 173902-34-6P 173902-35-7P
173902-36-8P 173902-37-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyridyl-substituted sulfonamides as selective **.beta. 3 adrenergic receptor** agonists for the treatment of type II diabetes and obesity)

L130 ANSWER 14 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:494735 HCAPLUS
DN 125:221588
TI Substituted sulfonamides as selective .beta.3 agonists for the treatment of diabetes and obesity
IN Fisher, Michael H.; Naylor, Elizabeth M.; Weber, Ann E.
PA Merck and Co., Inc., USA
SO U.S., 29 pp., Cont.-in-part of U.S. Ser. No. 233,166,abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	US 5541197	A	19960730		US 1995-404566	19950321	<--
	IL 113410	A1	19991130		IL 1995-113410	19950418	<--
	CA 2187932	AA	19951102		CA 1995-2187932	19950421	<--
	WO 9529159	A1	19951102		WO 1995-US4956	19950421	<--
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, US, US, UZ						
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG						
	AU 9523937	A1	19951116		AU 1995-23937	19950421	<--
	AU 687558	B2	19980226				
	EP 757674	A1	19970212		EP 1995-917116	19950421	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE						
	CN 1149869	A	19970514		CN 1995-192821	19950421	<--
	HU 76442	A2	19970929		HU 1996-2951	19950421	<--
	JP 09512275	T2	19971209		JP 1995-527797	19950421	<--
	JP 3149186	B2	20010326				
	ZA 9503336	A	19960109		ZA 1995-3336	19950425	<--
	FI 9604314	A	19961025		FI 1996-4314	19961025	<--
	NO 9604548	A	19961223		NO 1996-4548	19961025	<--
PRAI	US 1994-233166	B2	19940426	<--			
	US 1995-404565	A	19950321	<--			
	US 1995-404566	A	19950321	<--			
	WO 1995-US4956	W	19950421	<--			

OS MARPAT 125:221588
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Substituted sulfonamides I wherein: n is 0-5; m is 0 or 1; p is 0-3; ring A is (1) a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, (2) a benzene ring fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, (3) a 5 or 6-membered heterocyclic ring with

from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen fused to a 5 or 6-membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen, (4) Ph, or (5) a benzene ring fused to a C3-8 cycloalkyl ring; R1 is, e.g., OH, oxo, halo; R2 and R3 are independently (1) hydrogen, (2) C1-C10 alkyl or (3) C1-C10 alkyl with 1 to 4 substituents selected from hydroxy, C1-C10 alkoxy, and halogen; X is(1) CH2, (2) CH2CH2, (3) CH:CH, or (4) CH2O; R4 and R5 are independently , e.g., hydrogen, C1-C10 alkyl, halogen; R6 is (1) hydrogen or (2) C1-C10 alkyl; R7 is Z-(R1a)n; R1a is, e.g., R1 (with proviso), C3-8 cycloalkyl, optionally substituted Ph; Z is, e.g., Ph, naphthyl, heterocyclic, are selective **.beta.3 adrenergic receptor** agonists with very little .beta.1 and .beta.2 **adrenergic receptor** activity and as such the compds. are capable of increasing lipolysis and energy expenditure in cells (no data). The compds. thus have potent activity in the treatment of Type II diabetes and obesity. The compds. can also be used to lower triglyceride levels and cholesterol levels or raise high d. lipoprotein levels or to decrease gut motility. In addn., the compds. can be used to reduced neurogenic inflammation or as antidepressant agents. Compns. and methods for the use of the compds. in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high d. lipoprotein levels or for increasing gut motility are also disclosed. Thus, e.g., ring cleavage of (R)-2-(tetrazolo[1,5-a]pyrid-6-yl)oxirane with 2-(4-aminophenyl)ethylamine followed by Boc protection afforded amino alc. II; chlorosulfonylation of N-hexyl-N'-phenylurea (from hexylamine + Ph isocyanate) provided N-hexyl-N'-(4-chlorosulfonylphenyl)urea III; coupling of II + III followed by deprotection afforded sulfonamide IV.

IT **173900-55-5P 173900-57-7P 173900-58-8P**
173900-59-9P 173900-60-2P 173900-61-3P
173900-62-4P 173902-22-2P 173902-24-4P
173902-26-6P 173902-30-2P 173902-31-3P
173902-32-4P 173902-33-5P 173902-34-6P
173902-35-7P 173902-36-8P 173902-37-9P
180973-82-4P 180973-83-5P 180973-84-6P
180973-85-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(substituted sulfonamides as selective .beta.3 agonists for the treatment of diabetes and obesity)

L130 ANSWER 15 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:343723 HCAPLUS
DN 125:75996
TI Effects of several putative **.beta.3-adrenoceptor** agonists on lipolysis in human omental adipocytes
AU Hoffstedt, J.; Loennqvist, F.; Shimizu, M.; Blaak, E.; Arner, P.
CS Department of Medicine, Huddinge University Hospital, Huddinge, S-14186, Swed.
SO International Journal of Obesity (**1996**), 20(5), 428-434
CODEN: IJOBDP; ISSN: 0307-0565
PB Stockton
DT Journal
LA English
AB Atypical **.beta.3-adrenoceptor** agonists have attained an increasing interest as potential drugs against obesity and diabetes. However, their pharmacol. actions on the native, human . **beta.3-adrenoceptor** are not well defined. In the present study, the lipolytic effects of several putative **.beta .3-adrenoceptor** agonists were investigated in human omental adipocytes. CL 316 243 and CGP 12177 had selective partial . **beta.3**-agonist effects (pD2 about 4 and 8, resp.); the latter drug is a .beta.1-/.beta.2-**adrenoceptor** blocker in addn.

to its .**beta.3-adrenoceptor** agonist activity. BRL 37344 and SM 11044 were also partial agonists, but with significant .beta.1 - and/or .beta.2-**adrenoceptor** agonist properties. Bucindolol, ZD 2079, ICI D7114 and SR 58611A were ineffective as lipolytic drugs. In addn., ICI D7114 was a non-selective .beta.1-/.beta.2-/.**beta.3-adrenoceptor** antagonist in human adipocytes. None of the .**beta.3-adrenoceptor** agonists tested is an ideal drug for therapeutic use in man (i.e. regarded as a selective and full agonist with high receptor potency). Only CL 316 243 may have a potential therapeutic role, although the potency is very low. CGP 12177 is useful as a ref. substance for human in vitro studies.

IT **90730-96-4**, BRL 37344 **178600-17-4**, ZD 2079
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(putative .**beta.3-adrenoceptor** agonists effect on lipolysis in human omental adipocytes in relation to obesity treatment)

L130 ANSWER 16 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:271822 HCAPLUS
DN 125:1405
TI Use of 2-hydroxy-2-phenylethylaminoethoxyphenylacetate as .**beta.3-adrenoceptor** agonists
IN Holloway, Brian R.; Howe, Ralph; Rao, Balbir S.
PA Zeneca Ltd., UK
SO U.S., 10 pp., Cont.-in-part of U.S. Ser. No. 889,186, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5502078	A	19960326	US 1993-57763	19930507 <--
PRAI GB 1991-11425	A	19910528 <--		
US 1992-889186	B2	19920528 <--		

OS CASREACT 125:1405; MARPAT 125:1405
AB 3,5-Substituted-C6H3-CH(OH)CH2NHCH2CH2O-p-C6H4-CH2CO2H and bioprecursors and pharmaceutically acceptable salts thereof are described as .**beta.3-adrenoceptor** agonists having anti-obesity, hypoglycemic and related therapeutic utilities. (R)-4-[2-[2-(3-chlorophenyl)-2-hydroxyethylamino]ethoxy]phenylacetic acid and its HCl salt are claimed.
IT **146520-46-9P 146520-47-0P 146520-48-1P 146520-50-5P 146520-51-6P 146520-52-7P 146520-53-8P 146520-54-9P 177288-18-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(2-hydroxy-2-phenylethylaminoethoxyphenylacetates as .**beta.3-adrenoceptor** agonists)

L130 ANSWER 17 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:203512 HCAPLUS
DN 124:278730
TI Biphasic effects of the .beta.-adrenoceptor agonist, BRL 37344, on glucose utilization in rat isolated skeletal muscle
AU Liu, Yong-Ling; Cawthorne, Michael A.; Stock, Michael J.
CS Dep. Physiol., St. George's Hosp. Med. Sch., London, SW17 0RE, UK
SO British Journal of Pharmacology (**1996**), 117(6), 1355-61
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton

DT Journal
LA English
AB The effects of the selective .**beta.3-adrenoceptor** agonist, BRL 37344 (BRL) on glucose uptake and phosphorylation (i.e. glucose utilization; GU) and glycogen synthesis in rat isolated soleus and extensor digitorium longus (EDL) muscle prepns. in vitro were investigated by use of 2-deoxy-[3H]-glucose (GU) and [U-14C]-glucose (glycogen synthesis). Low concns. of BRL (10-11-10-9 M) significantly increased GU, with maximal increases of 30% in soleus and 24% in EDL at 10-11 M. Neither the selective .beta.1-**adrenoceptor** antagonist, atenolol (10-8-10-6 M), nor the selective .beta.2-**adrenoceptor** antagonist, ICI 118551 (10-8-10-6 M) had any effect on the stimulation of GU induced by 10-11 M BRL. High concns. of BRL (10-6-10-5 M) caused significant inhibition (up to 30%) of GU in both soleus and EDL muscles. The inhibition at 10-6 M BRL was blocked completely by 10-6 and 10-7 M ICI 118551 in soleus, and by 10-6-10-8 M ICI 118551 in EDL; atenolol (10-8-106 M) had no effect. Another selective .**beta.3-adrenoceptor** agonist, CL 316,243, also caused a significant stimulation of muscle GU, with maximal increases of 43% at 10-9 M in soleus and 45% at 10-10 M in EDL. The stimulation of GU declined with further increases in the concn. of CL 316,243, but no inhibition of GU was seen, even at the highest concn. (10-5 M) tested. BRL at 10-5 M inhibited completely insulin-stimulated glycogen synthesis in both soleus and EDL, but this inhibitory effect of BRL was abolished by 10-6 M ICI 118551. BRL at 10-11 M (with or without 10-6 M ICI 118551) had no effect on insulin-stimulated glycogen synthesis. It is concluded that: (i) low (<nM) concns. of BRL stimulate GU via an atypical .beta.-**adrenoceptor** that is resistant to conventional .beta.1-**adrenoceptor** and .beta.2-**adrenoceptor** antagonists; (ii) the stimulation of GU is negated by the activation of .beta.2-**adrenoceptors** that occurs at higher (>nM) concns. of BRL; (iii) inhibition of GU via .beta.2-**adrenoceptor** activation is assocd. with inhibition of glycogen synthesis, possibly due to activation of glycogenolysis; (i.v.) the opposing effects of .beta.2-**adrenoceptor** and atypical .beta.-**adrenoceptor** activation on GU suggest that in skeletal muscle these **adrenoceptors** are linked to different post-receptor pathways.
IT **90730-96-4**, BRL37344
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(biphasic effects of the .beta.-adrenoceptor agonist, BRL 37344, on glucose utilization in rat isolated skeletal muscle)

L130 ANSWER 18 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:94552 HCAPLUS
DN 124:194133
TI Comparison of the profiles of agonists as stimulants of the .**beta.3-adrenoceptor** in vitro with their gastroprotective effects in the conscious rat
AU Bahl, A. K.; Clayton, N. M.; Coates, J.; Martin, D. P.; Oakley, I. G.; Strong, P.; Trevethick, M. A.
CS Glaxo Wellcome Research & Development Ltd., Glaxo Wellcome Medicines Centre, Stevenage, Herts, SG1 2NY, UK
SO British Journal of Pharmacology (**1996**), 117(3), 580-6
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB This paper compares the activity of a range of agonists as stimulants of the .**beta.3-adrenoceptor** in rat isolated esophagus with their ability to afford protection against indomethacin-induced gastric damage in the conscious rat. The .

beta.3-adrenoceptor agonists, CL 316243 and BRL 37344, the non-selective .beta.-**adrenoceptor** agonist, isoprenaline and the selective .beta.2-**adrenoceptor** agonist, salmeterol, all evoked concn.-dependent relaxation of precontracted muscularis mucosa from rat esophagus. The rank order of agonist potency was BRL 37344 > CL 316243 > isoprenaline .mchgt. salmeterol. The selective .beta.1-**adrenoceptor** agonist, denopamine, did not relax the prepn. The relaxant responses to all agonists were resistant to blockade by atenolol (10 .mu.M), and ICI 118551 (1 .mu.M) thus suggesting that they were not mediated by either .beta.1- or .beta.2-**adrenoceptor** stimulation. In contrast, cyanopindolol and propranolol did inhibit responses to BRL 37344, CL 316243 and isoprenaline, giving pA2 values or pKB ests. which were consistent with an interaction of .**beta.3-adrenoceptors** (i.e. approx. 8.0 and 6.5 resp.). However, responses to salmeterol were resistant to blockade by all the antagonists tested, which suggests that the high (>1 .mu.M) concns. of salmeterol used exerted non-specific relaxant effects. The agonist effects of CL 316243 and BRL 37344 on .beta.1- and .beta.2-**adrenoceptors** were assessed on guinea-pig right atrium and precontracted trachea resp. Both agonists had minimal activity as stimulants of heart rate, but did relax trachea, being 380 (CL 316243) and 21 (BRL 37344) fold less potent than isoprenaline. CL 316243 and BRL 37344 were potent inhibitors of indomethacin-induced gastric antral ulceration in the conscious rat (ED50 values = 0.24 and 0.09 .mu.mol kg-1 p.o.) ABA: Salmeterol was approx. 100 times less potent than BRL 37344 as a gastroprotective agent and denopamine was without effect. The gastroprotective effects of CL 316243 and BRL 37344 were resistant to blockade by ICI 118551 (10 mg kg-1, p.o.) and propranolol (10 mg kg-1 p.o.). In contrast, both antagonists caused dose-related inhibition of the protective action of salmeterol (10 mg kg-1, p.o.). Cyanopindolol was not assessed as an antagonist in vivo because preliminary expts. revealed that it exacerbated indomethacin-induced gastric damage in its own right. In conclusion, the .**beta.3-adrenoceptor** agonists CL 316243 and BRL 37344 were potent inhibitors of indomethacin-induced gastric antral ulceration in the rat. These data suggest that an agonist which is potent and selective for the human .**beta.3-adrenoceptor** may confer mucosal protection in man.

IT **71771-90-9**, Denopamine **90730-96-4**, BRL 37344
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(comparison of profiles of agonists as stimulants of .**beta.3-adrenoceptor** in vitro with gastroprotective effects in conscious rat)

L130 ANSWER 19 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:998182 HCAPLUS
DN 124:176115
TI Preparation of substituted arylsulfonamides as selective .beta.3 agonists for the treatment of diabetes and obesity.
IN Fisher, Michael H.; Naylor, Elisabeth M.; Ok, Dong; Weber, Ann E.; Shih, Thomas; Ok, Hyun
PA Merck and Co., Inc., USA
SO PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9529159	A1	19951102	WO 1995-US4956	19950421 <--

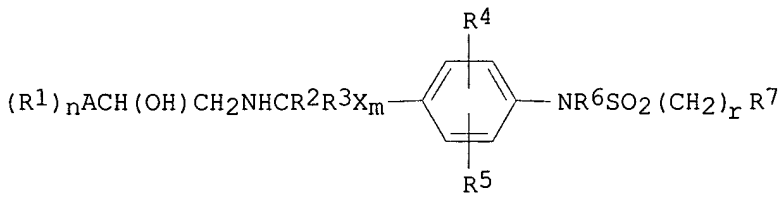
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG,

KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG,
SI, SK, TJ, TT, UA, US, US, US, UZ
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT,
LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE,
SN, TD, TG

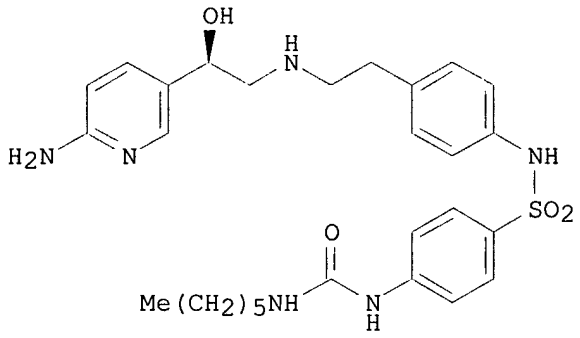
US 5541197	A	19960730	US 1995-404566	19950321	<--	
AU 9523937	A1	19951116	AU 1995-23937	19950421	<--	
AU 687558	B2	19980226				
EP 757674	A1	19970212	EP 1995-917116	19950421	<--	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE						
JP 09512275	T2	19971209	JP 1995-527797	19950421	<--	
JP 3149186	B2	20010326				
FI 9604314	A	19961025	FI 1996-4314	19961025	<--	
NO 9604548	A	19961223	NO 1996-4548	19961025	<--	
PRAI US 1994-233166	A	19940426	<--			
US 1995-404565	A	19950321	<--			
US 1995-404566	A	19950321	<--			
WO 1995-US4956	W	19950421	<--			

OS MARPAT 124:176115

GI



I



II

AB Title compds. [I; m = 0, 1; n = 0-5; r = 0-3; A = heterocyclyl, benzoheterocyclyl, heterocycloheterocyclyl, Ph, benzocycloalkyl; R1 = OH, O, halo, cyano, amino, CF3, sulfonylamino, (substituted) alkyl, etc.; R2, R3 = H, (substituted) alkyl; R4, R5 = H, alkyl, halo, amino, sulfonylamino, OH, etc; R6 = H, alkyl; R7 = Z(R11)n; R11 = R1, provided that when A = Ph, R11 .noteq. alkyl; X = CH2, CH2CH2, CH:CH, CH2O; Z = Ph, naphthyl, heterocyclyl, heterocycloheterocyclyl] were prepd. as selective **.beta.3 adrenergic receptor** agonists with very little .beta.1 and .beta.2 **adrenergic receptor** activity which are capable of increasing lipolysis and energy expenditure in cells (no data). The compds. thus have potent activity in the treatment of Type II diabetes and obesity. The compds. can also be used to lower triglyceride levels and cholesterol levels or raise high d. lipoprotein levels or to decrease gut motility. In addn., the compds. can be used to reduce neurogenic inflammation or as antidepressant agents. Title compd. (II) was prepd. in several steps.

IT **173900-52-2P 173900-53-3P 173900-54-4P**
173900-55-5P 173900-56-6P 173900-57-7P
173900-58-8P 173900-59-9P 173900-60-2P
173900-61-3P 173900-62-4P 173902-22-2P
173902-24-4P 173902-26-6P 173902-30-2P
173902-31-3P 173902-32-4P 173902-33-5P
173902-34-6P 173902-35-7P 173902-36-8P
173902-37-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted sulfonamides as selective .beta.3 agonists for the treatment of diabetes and obesity)

L130 ANSWER 20 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:614635 HCAPLUS
DN 123:74228
TI Predictive quantitative structure-activity relationships (QSAR) analysis of .beta.3-adrenergic ligands
AU Blin, Nathalie; Federici, Christian; Koschielniak, Thiery; Strosberg, Donny
CS Institut Cochin Genetique Moleculaire, Universite Paris VII, Paris, 75014, Fr.
SO Drug Design and Discovery (**1995**), 12(4), 297-311
CODEN: DDDIEV; ISSN: 1055-9612
PB Harwood
DT Journal
LA English
AB A novel quant. structure-activity relationships strategy was used to analyzed seventeen .beta.-adrenergic ligands for which we had previously evaluated pharmacol. properties in Chinese hamster ovary cells transfected with the human .beta.1-, .beta.2- or .beta.3-adrenergic gene (Blin et al., 1993, Mol. Pharmacol., 44: 1094-1104). These ligands were classified into pharmacol. activity categories in order to det. the extent to which mol. structural features may be involved in the selectivity of the interaction with the .beta.3-AR, or to define mol. features and properties characteristic of a .beta.3-AR high affinity ligand or of a potent .beta.3-adrenergic agonist. Topol. and physico-chem. mol. descriptors were obtained using a novel software combining calcns. with multivariate statistical methods, such as principal component anal. and discriminant anal. This study showed that .beta.1/.beta.2-antagonists .beta.3-agonists could be differentiate from .beta.1/.beta.2/.beta.3-agonists on the basis of their topol. mol. descriptors weighted by partial at. charge and lipophilicity logP values. Bulky lipophilic groups at the end of the alkylamine chain and an ethoxy function, extending the flexible portion of the mol. and modifying the electron d. distribution, were requirements for selective agonism at the .beta.3-site. Charge and logP weighted 2D-autocorrelation vectors were properties able to discriminate between classes of agonists to terms of their affinity, potency or intrinsic activity, thus emphasizing the part these mol. descriptors play in detg. .beta.3-adrenergic ligands. These results, in assocn. with the powerful activity-prediction model evaluated in the test, provide a framework to rationalize the synthesis of new .beta.3-AR specific compds.
IT **74248-92-3**, LY 79771 **90730-96-4**, BRL 37344
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(QSAR anal. of .beta.3-adrenergic ligands)

L130 ANSWER 21 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:528146 HCAPLUS
DN 122:281934
TI Metabolic alterations associated with the antidiabetic effect of .

beta.3-adrenergic receptor agonists
in obese mice
AU Arbeeny, Cynthia M.; Meyers, Daniel S.; Hillyer, Donna E.; Bergquist, Kristin E.
CS Dep. Metabolic Diseases, Bristol-Myers Squibb Pharmaceutical Res. Inst., Princeton, NJ, 08543-4000, USA
SO American Journal of Physiology (**1995**), 268(4, Pt. 1), E678-E684
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB Treatment of obese (ob/ob) mice with the **.beta.3-adrenergic receptor** (**.beta.3**-AR) agonist BRL-35135 (1 mg.cntdot.kg body wt-1.cntdot.day-1 for 20 days) normalized plasma glucose levels and significantly decreased plasma insulin and nonesterified fatty acid levels. The time frame for the hypoglycemic effect, which reached a max. after 10 days of treatment, paralleled an increase in brown adipose tissue DNA and protein content. The basal level of mRNA for the **.beta.3**-AR and mitochondrial uncoupling protein was found to be markedly decreased in the ob/ob animals relative to the lean group. Chronic treatment of ob/ob mice for 20 days resulted in a twofold increase in **.beta.3**-AR mRNA and a fivefold increase in uncoupling protein mRNA in brown adipose tissue relative to the placebo group. These findings indicate that chronic treatment of ob/ob animals with a **.beta.3**-AR agonist results in proliferation of brown adipose tissue, with an upregulation of the **.beta.3**-AR, which is assocd. with a decrease in plasma glucose, insulin, and nonesterified fatty acid levels.
IT **86615-96-5**, BRL-35135
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(metabolic alterations assocd. with antidiabetic effect of .beta.3-adrenergic agonist BRL-35135 in obese mice)

L130 ANSWER 22 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:396436 HCAPLUS
DN 122:178252
TI Acute effects of the **.beta.3-adrenoceptor** agonist, BRL 35135, on tissue glucose utilization
AU Liu, Yong-Ling; Stock, Michael J.
CS Dep. Physiol., St. George's Hosp. Med. Sch., London, SW17 0RE, UK
SO British Journal of Pharmacology (**1995**), 114(4), 888-94
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB The acute effects of BRL 35135 (BRL) on tissue glucose utilization index (GUI) in vivo were investigated in anesthetized rats by use of 2-deoxy-[3H]-glucose. I.v. injection of BRL caused a dose-dependent increase in GUI in skeletal muscle, and white and brown adipose tissue; plasma insulin and fatty acid concns. were also increased. Chronic treatment with BRL added to the diet caused a 34 fold increase in basal GUI of brown adipose tissue (BAT), but had no effect on GUI in other tissues. After chronic treatment, the acute tissue response to an i.v. maximal dose of BRL had disappeared completely in all tissues apart from the soleus muscle. A high dose (20 mg kg-1) of the non-selective .beta.-antagonist, propranolol, inhibited the acute effect of BRL on GUI in BAT, but failed to affect GUI in muscle. A lower dose (1 mg kg-1) of the antagonist also inhibited the BAT response, but had little or no effect on the response in Type I (working) muscles such as soleus and adductor longus (ADL), and potentiated the response in Type II

(non-working) muscles such as tibialis and extensor digitorium longus (EDL). A low dose (1 mg kg-1) of the selective .beta.1-antagonist, atenolol, had no effect on the BRL response but the same dose of the selective .beta.2-antagonist, ICI 118551, potentiated significantly the effect of BRL on GUI in most muscles without altering plasma insulin levels. It is concluded that: (i) the heterogeneous tissue responses of different muscle fiber types in the presence of .beta.-antagonists indicates that BRL affects muscle GUI directly, in addn. to effects mediated by increases in plasma insulin concn.; (ii) the resistance of the BRL response to conventional .beta.-adrenoceptor antagonists implicates an atypical adrenoceptor mediating the GUI response in skeletal muscle, but this may not be identical to the adipose tissue .beta.2-adrenoceptor, (iii) the potentiation of BRL responses by ICI 118551 indicates an inhibitory .beta.2-adrenoceptor-mediated component in the muscle GUI response to BRL.

IT **86615-96-5**, BRL 35135
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(acute effects of the **.beta.3-adrenoceptor** agonist BRL 35135 on tissue glucose utilization)

L130 ANSWER 23 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:252043 HCAPLUS
DN 122:23562
TI Potentiation of the antiobesity effect of the selective **.beta.3-adrenoceptor** agonist BRL 35135 in obese Zucker rats by exercise
AU Santti, Eriika; Huupponen, Risto; Rouru, Juha; Haenninen, Virve; Pesonen, Ullamari; Jhanwar-Uniyal, Meena; Koulu, Markku
CS Dept. Pharmacology, Univ. Turku, Turku, Finland
SO British Journal of Pharmacology (**1994**), 113(4), 1231-6
CODEN: BJPCBM; ISSN: 0007-1188
PB Stockton
DT Journal
LA English
AB The effects of chronic treatments with a selective **.beta.3-adrenoceptor** agonist and a selective .alpha.2-**adrenoceptor** antagonist and their interactions with phys. exercise training were studied in exptl. obesity. BRL 35135 (**.beta.3**-agonist, 0.5 mg/kg/day, orally), atipamezole (.alpha.2-antagonist, 4.0 mg/kg/day, orally) and placebo were given to genetically obese male Zucker rats. Half of the rats were kept sedentary whereas the other half were subjected to moderate treadmill exercise training. Boty wt. gain, cumulative food intake, the neuropeptide Y content of the hypothalamic paraventricular nucleus, brown adipose tissue thermogenic activity (measured as GDP binding), and plasma insulin and glucose levels were measured after 3-wk treatment and exercise. Treatment with BRL 35135 reduced wt. gain by 19%, increased brown adipose tissue thermogenic activity 45-fold and reduced plasma insulin by 50%. Atipamezole slightly increased food intake and neuropeptide Y content in the paraventricular hypothalamic nucleus but had no effect on the other parameters measured. Exercise alone had no effect on wt. gain, food intake or thermogenic activity, whereas it reduced plasma insulin and glucose levels. The effect of BRL 35135 on wt. gain and thermogenic activity was potentiated by exercise: the redn. in wt. gain was 56% in comparison with 19% in sedentary animals. Food intake was reduced in the BRL 35135-treated-exercise-trained animals, although neither the **.beta.3**-agonist nor exercise alone affected it. Based on these results in genetically obese Zucker rats, combination of **.beta.3**-agonist treatment with a moderate phys. training may offer a new feasible approach to the therapy of obesity.

IT **86615-96-5**, BRL 35135

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(.beta.3-adrenergic agonist BRL 35135 plus exercise treatment of obesity)

L130 ANSWER 24 OF 24 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:645501 HCAPLUS
DN 121:245501
TI Enhancement of gastric mucosal blood flow by beta-3 adrenergic agonists prevents indomethacin-induced antral ulcer in the rat
AU Kuratani, Kazuyoshi; Kodama, Hiroshi; Yamaguchi, Isamu
CS Tsukuba Res. Labs., Fujisawa Pharm. Co. Ltd., Tsukuba, 300-26, Japan
SO Journal of Pharmacology and Experimental Therapeutics (**1994**), 270(2), 559-65
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
AB Indomethacin (32 mg/kg s.c.) produced mainly antral ulcers in refed rats but almost exclusively corpus erosions in fasted rats. S.c. doses of a nonselective beta (isoproterenol), a selective .beta.-2 (salbutamol) and selective .**beta**.-**3** adrenergic agonists BRL 35135, CL 316243, SR 58611A, dose-dependently attenuated the antral ulcers, and their activities were in the order of BRL 35135 (ED50 = 0.03 mg/kg) > CL 316243 (ED50 = 0.04 mg/kg) > SR 68511A (ED50 = 0.2 mg/kg) > isoproterenol (ED50 = 0.4 mg/kg) > salbutamol (ED50 = 6 mg/kg). Whereas only isoproterenol, salbutamol and BRL35135 significantly attenuated the corpus erosions and reduced gastric acid secretion in pylorus-ligated rats. In in vitro, all the beta agonists enhanced the beating rate of guinea pig atria (.beta.-1 action) and inhibited spontaneous contractions of rat uterus (.beta.-2 action) and colon (.**beta**.-**3** action). There was found a statistically significant correlation between the IC50 values of the drugs on the colon and ED50 values on the indomethacin-induced antral ulcers (r = 0.97). In addn., the beta agonists excepting salbutamol increased antral gastric mucosal blood flow in rats anesthetized with halothane, and the activities were arranged in the potency order of inhibiting colon motility. It is concluded that activation of .**beta**.-**3 adrenoceptor** attenuates the indomethacin-induced antral ulcers through an enhancement of antral gastric mucosal blood flow, whereas activation of beta-1 and/or .beta.-2 **adrenoceptors** attenuates indomethacin-induced corpus erosions through an inhibition of gastric secretion.
IT **86615-96-5**, BRL 35135
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(enhancement of gastric mucosal blood flow by beta-3 adrenergic agonists prevents indomethacin-induced antral ulcer in rat)

=> d bib abs hitrn retable tot l119

L119 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2002 ACS
AN 1986:224720 HCAPLUS
DN 104:224720
TI Tertiary 2-hydroxy-3-aryloxypropyl- and 2-hydroxy-2-benzofuranylethylamines having antihyperglycemic and/or antiobesity activity
IN Ainsworth, Anthony Trevor; Cawthorne, Michael Anthony
PA Beecham Group PLC, UK
SO Eur. Pat. Appl., 94 pp.
CODEN: EPXXDW
DT Patent

LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	EP 170121	A1	19860205		EP 1985-108609	19850710	<--
	EP 170121	B1	19910619				
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE						
	AT 64590	E	19910715		AT 1985-108609	19850710	<--
	DK 8503253	A	19860120		DK 1985-3253	19850717	<--
	ZA 8505400	A	19860528		ZA 1985-5400	19850717	<--
	JP 61076446	A2	19860418		JP 1985-157137	19850718	<--
	ES 545365	A1	19861116		ES 1985-545365	19850718	<--
	AU 8545173	A1	19860123		AU 1985-45173	19850719	<--
	ES 552860	A1	19870501		ES 1986-552860	19860310	<--
PRAI	GB 1984-18472		19840719	<--			
	EP 1985-108609		19850710	<--			

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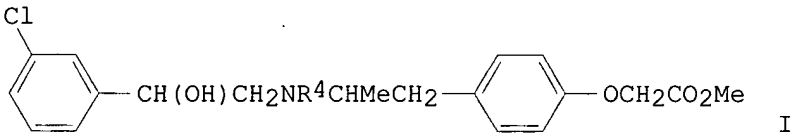


I

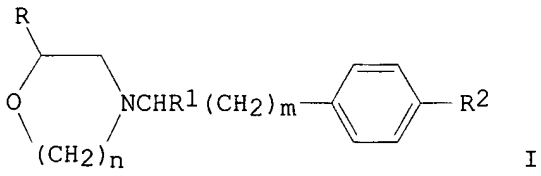
AB NR1R2R3 [R1 = (un)substituted 2-hydroxy-3-aryloxypropyl, 2-hydroxy-2-benzofuranylethyl; R2 = as given for R1, (un)substituted 2-hydroxy-2-arylethyl; R3 = substituted 2- or 3-arylpropyl, 2-aryloxyethyl; CHOH moieties may be present as carbonyls or esters] were prepd. as antiobesity and/or antihyperglycemia agents in humans or animals, and as feed additives for livestock. Thus, aminopropylphenoxyacetate (.+-.)-(R*,R*)-I (R4 = H) was refluxed with phenoxymethyloxirane in EtOH for 4 days to give I [R4 = CH2CH(OH)CH2OPh] (II). Given orally to mice, II reduced parametrial fat pads by 39% at 55 mg/kg, increased energy expenditure by 58% at 27.5 mg/kg, and gave 50% redn. in 2-h integrated blood glucose curves at 0.5 .mu.mol/kg.

IT **102198-54-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, with phenoxymethyloxirane)

L119 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2002 ACS
AN 1985:523489 HCAPLUS
DN 103:123489
TI Morpholine derivatives
IN Cantello, Barrie Christian Charles
PA Beecham Group PLC, UK
SO Eur. Pat. Appl., 36 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 140359	A1	19850508	EP 1984-113014	19841029
	EP 140359	B1	19890125		
	R: CH, DE, FR, GB, IT, LI, NL				
	US 4607033	A	19860819	US 1984-666818	19841031
	JP 60112778	A2	19850619	JP 1984-231130	19841101
	JP 06004604	B4	19940119		
	US 4665072	A	19870512	US 1986-865348	19860521
	US 4783460	A	19881108	US 1987-26893	19870317

PRAI GB 1983-29247 19831102
GB 1984-4047 19840216
US 1984-666818 19841031
US 1986-865348 19860521
GI



I

AB Morpholines and perhydrooxazepines I [n = 2, 3; R = Ph, halophenyl, (trifluoromethyl)phenyl, 2-benzofuryl; R1 = H, Me; m = 1, 2; R2 = CO2H, esterified CO2H, carbamoyl, carboxyalkoxy, esterified carboxyalkoxy, carbamoylalkoxy, aminoalkoxy, hydroxyalkoxy, alkoxyalkoxy], which were prepd., exhibited antidiabetic activity. 2-Phenylmorpholine was stirred with 4-(MeCOCH2)C6H4OCH2CO2Me and NaB(CN)H3 in MeOH, and the mixt. was worked up to give I (n = 2, R = Ph, R1 = Me, m = 1, R2 = OCH2CO2Me).
IT **98235-69-9P 98235-70-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

L119 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2002 ACS
AN 1984:406799 HCAPLUS
DN 101:6799
TI 2-Aminoethyl ether derivatives, and their pharmaceutical compositions
IN Cantello, Barrie Christian Charles
PA Beecham Group PLC, UK
SO Eur. Pat. Appl., 87 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	EP 99707	A1	19840201		EP 1983-303983	19830708	<--
	EP 99707	B1	19861210				
	R: BE, CH, DE, FR, GB, IT, LI, NL, SE						
	AU 8316826	A1	19840223		AU 1983-16826	19830714	<--
	AU 557743	B2	19870108				
	ZA 8305126	A	19840627		ZA 1983-5126	19830714	<--
	US 4629737	A	19861216		US 1983-513869	19830714	<--
	CA 1253870	A1	19890509		CA 1983-432465	19830714	<--
	JP 59031740	A2	19840220		JP 1983-128035	19830715	<--
	ES 524174	A1	19841116		ES 1983-524174	19830715	<--
PRAI	GB 1982-20645		19820716	<--			
	GB 1982-28753		19821007	<--			
	GB 1982-35672		19821215	<--			

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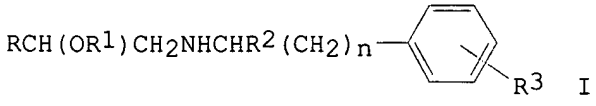


I

AB Amines I [R = Ph, alkyl-, halo-, or (trifluoromethyl)phenyl, PhOCH2, 2-benzofuryl; R1 = alkyl, phenylalkyl; R2 = H, Me; n = 1, 2; R3 = CO2H, carboxyalkyl, carboxyalkenyl, hydroxyalkyl, hydroxyalkenyl, aminoalkyl, aminoalkenyl, alkoxy, alkylthio, alkylamino, hydroxyalkoxy, hydroxyalkylthio, hydroxyalkylamino, aminoalkoxy, aminoalkylthio, aminoalkylamino, ZZ1CO2H (Z = O, S, NH; Z1 = alkylene, alkenylene)] were prepd., and they exhibited antidiabetic activity. A mixt. of 4-(MeCOCH2)C6H4OCH2CO2Me and 3-ClC6H4CH(OMe)CH2NH2 in PhMe was refluxed 2 h, and the mixt. was treated with Pt and H2 to give I (R = 3-ClC6H4, R1 = R2 = Me, n = 1, R3 = 4-OCH2CO2Me). Some I also showed antiinflammatory activity and inhibited blood platelet aggregation.

IT **90469-95-7P 90469-96-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and amidation of, by methylamine)

IT **90469-90-2P 90469-91-3P 90469-93-5P**
90469-94-6P
RL: **BAC (Biological activity or effector, except adverse)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and antidiabetic activity of)

L119 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2002 ACS
AN 1983:594608 HCAPLUS
DN 99:194608
TI Secondary phenylethanol amines and their pharmaceutical application
IN Hindley, Richard Mark
PA Beecham Group PLC, UK
SO Eur. Pat. Appl., 109 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 70133	A2	19830119	EP 1982-303507	19820705 <--
	EP 70133	A3	19830518		
	EP 70133	B1	19860514		
	R: BE, CH, DE, FR, GB, IT, LI, NL, SE				
	AU 8285790	A1	19830120	AU 1982-85790	19820709 <--
	AU 553070	B2	19860703		
	ZA 8204903	A	19830427	ZA 1982-4903	19820709 <--
	JP 58018339	A2	19830202	JP 1982-121097	19820712 <--
	ES 513967	A1	19830801	ES 1982-513967	19820712 <--
	ES 520690	A1	19840501	ES 1983-520690	19830316 <--
	ES 520691	A1	19840501	ES 1983-520691	19830316 <--
PRAI	GB 1981-21442		19810711 <--		
	GB 1981-39024		19811230 <--		

AB HOCHRCH2NHCR1R2(CH2)nR3 [I; R = (un)substituted Ph, 2-benzofuranyl; R1, R2 = H, Me; R3 = substituted alkoxyphenyl; n = 1, 2] were prepd. Thus, 3,2-ClFC6H3CH(OH)CH2NH2 was condensed with 4-(MeNHCH2CH2O)C6H4CH2COMe to give an enamine which was hydrogenated to give diastereoisomeric 3,2-ClFC6H3CH(OH)CH2NHCHMeCH2C6H4(OCH2CH2NHMe)-4.2HCl (II). In mice, 1 .mu.mol II/kg orally reduced blood glucose 64%, and 25.3 mg II/kg orally increased energy expenditure 48% and reduced food intake 21%.

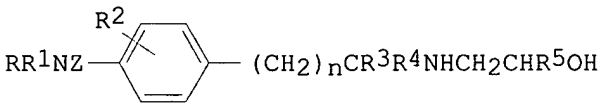
IT **86608-15-3P 86608-16-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and antidiabetic and antiobesity activity of)

L119 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2002 ACS
AN 1983:215308 HCAPLUS
DN 98:215308
TI Secondary amines
IN Smith, David Glynn

PA Beecham Group PLC, UK
SO Eur. Pat. Appl., 89 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 61907	A1	19821006	EP 1982-301594	19820326 <--
	EP 61907	B1	19840801		
	R: BE, CH, DE, FR, GB, IT, NL, SE				
	AU 8282123	A1	19821007	AU 1982-82123	19820329 <--
	ZA 8202124	A	19830126	ZA 1982-2124	19820329 <--
	JP 57176934	A2	19821030	JP 1982-52194	19820330 <--
	ES 510982	A1	19830501	ES 1982-510982	19820330 <--
	ES 518978	A1	19840301	ES 1983-518978	19830113 <--
PRAI	GB 1981-10036		19810331 <--		
	GB 1981-39023		19811230 <--		

GI



I

AB Ethanolamines I [R, R1 = H, alkyl, (un)substituted PhCH2; R2 = H, halogen, alkoxy, alkyl, NR6R7; R3, R4 = H, Me; R5 = (un)substituted Ph, 2-benzofuranyl; R6 = H, alkyl; R7 = alkyl; Z = alkylene; n = 1,2] were prepd. Thus, 4.11 g HOCHPhCH2NH2 was treated with 4.77 g 4-NCC6H4CH2COMe and the resulting enamine reduced with NaBH4 and then with LiAlH4 to give 3.8 g I (R, R2, R3, R5 = H, R1 = R4 = Me, Z = CH2, n = 1). I are active as appetite depressants at 6.3-12.2 mg/kg, hypoglycemics (2.5-100 mg/kg), inflammation inhibitors, and are >60 times as effective as aspirin in inhibiting blood platelet aggregation.

IT **85064-67-1P 85070-73-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and antiobesity activity of)

IT **85114-96-1P 85114-97-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction with methylamine)

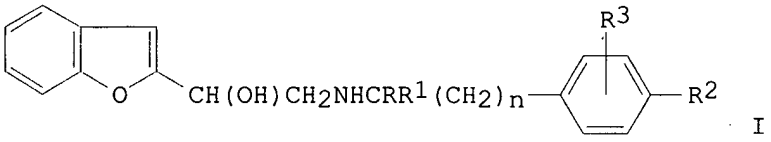
IT **85064-68-2P 85070-97-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and redn. of)

L119 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2002 ACS
AN 1982:544754 HCAPLUS
DN 97:144754
TI Secondary amines
IN Ferris, Michael John
PA Beecham Group Ltd. , UK
SO Brit. UK Pat. Appl., 14 pp.
CODEN: BAXXDU
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 2084577	A	19820415	GB 1981-28824	19810923 <--

GB 2084577	B2	19840502			
CA 1175851	A1	19841009	CA 1981-385953	19810915	<--
ZA 8106567	A	19820929	ZA 1981-6567	19810922	<--
AU 8175603	A1	19820401	AU 1981-75603	19810923	<--
AU 546104	B2	19850815			
EP 51917	A1	19820519	EP 1981-304398	19810923	<--
EP 51917	B1	19860219			
R: BE, CH, DE, FR, IT, NL					
US 4432993	A	19840221	US 1981-305117	19810924	<--
JP 57085383	A2	19820528	JP 1981-151924	19810925	<--
ES 505801	A1	19830201	ES 1981-505801	19810925	<--

PRAI GB 1980-31228 19800926 <--
OS CASREACT 97:144754
GI



I

AB Benzofurylethanolamines I [R, R1 = H, Me; R2 = OH, (un)substituted alkoxy, alkyl; R3 = H, OH, halogen, alkyl, alkoxy; n = 1-3] were prepd. Thus 2-formylbenzofuran was treated with Me3SiCN and reduced with LiAlH4 to give 2-(2-benzofuryl)-2-hydroxyethylamine which was treated with 4-MeC6H4CH2COMe and hydrogenated to give I (R = Me, R1 = R3 = H, R2 = Me, n = 1, II) as a mixt. of diastereoisomers. II had antiobesity activity with only a slight effect on heart rate. Other I had antidiabetic, antiinflammatory, and platelet aggregation-inhibiting activity.

IT **83123-40-4 83123-48-2**
RL: RCT (Reactant)
(hydrogenation of)

IT **83123-24-4P 83123-29-9P 83123-30-2P**
83123-31-3P 83123-32-4P 83123-35-7P
83123-41-5P 83123-42-6P 83123-43-7P
83123-44-8P 83123-45-9P 83123-46-0P
RL: **BAC (Biological activity or effector, except adverse)**; SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and antiobesity and antidiabetic activity of)

IT **83123-24-4P 83123-25-5P 83123-26-6P**
83123-27-7P 83123-28-8P 83123-29-9P
83123-36-8P 83123-37-9P 83123-38-0P
83123-39-1P 83123-47-1P 83140-92-5P
RL: **BAC (Biological activity or effector, except adverse)**; SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and pharmacol. activity of)

L119 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2002 ACS
AN 1981:568976 HCAPLUS
DN 95:168976
TI Secondary ethanol amines, their use in pharmaceutical compositions and intermediates for them
IN Ferris, Michael John
PA Beecham Group Ltd. , UK
SO Eur. Pat. Appl., 43 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	EP 29320	A2	19810527	EP 1980-303931	19801105
	EP 29320	A3	19810805		
	EP 29320	B1	19850710		
	R: AT, BE, CH, DE, FR, GB, IT, NL, SE				
	AT 14222	E	19850715	AT 1980-303931	19801105
	US 4341793	A	19820727	US 1980-204846	19801107
	DK 8004891	A	19810516	DK 1980-4891	19801114
	JP 56083484	A2	19810708	JP 1980-160639	19801114
	ZA 8007078	A	19811028	ZA 1980-7078	19801114
	ES 496880	A1	19820216	ES 1980-496880	19801114
	CA 1161053	A1	19840124	CA 1980-364738	19801114
	AU 540343	B2	19841115	AU 1980-64354	19801118
	AU 8064354	A1	19810521		
	ES 507410	A1	19820901	ES 1981-507410	19811124
PRAI	GB 1979-39536		19791115		
	EP 1980-303931		19801105		

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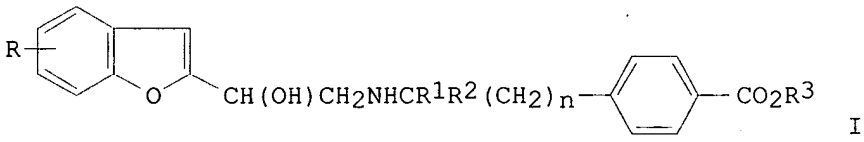

I

AB Benzofuranethanolamines I (R = H, Cl, Br, OH, OMe, NO2, NH2, CF3; R1, R2 = H, Me; R3 = H, alkyl; n = 1-3) were prepd. Thus, 4-MeO2CC6H4CH2CHMeNH2 was treated with 2-benzofuranglyoxal, followed by NaBH4 redn. to give I (R = R1 = H, R2 = R3 = Me, n = 1) as a 4:1 mixt. of diastereoisomers. The isomers gave 27.4 and 46.4% redn. in blood glucose, resp., at 1.0 and 17.7 mg/kg, resp., orally in mice.

IT **79361-97-0P 79362-71-3P 79362-73-5P**
79362-74-6P 79362-76-8P 79362-77-9P
79362-78-0P 79362-80-4P 79362-81-5P
79362-82-6P 79362-89-3P 79362-90-6P
79390-97-9P 79390-98-0P
RL: **BAC (Biological activity or effector, except adverse)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and antidiabetic activity of)

L119 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2002 ACS
AN 1966:104078 HCAPLUS
DN 64:104078
OREF 64:19560g-h,19561a
TI Benzofuran derivatives
PA Societe Belge de l'Azote et des Produite Chimiques du Marly, S.A.
SO 9 pp.
DT Patent
LA Unavailable
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	NL 65006415		19651122	NL	
PRAI	GB		19640520		

GI For diagram(s), see printed CA Issue.

AB The title compds. were prepd. through reaction of I (R = halogen) with an amine. Thus, 30 g. 2-(.omega.-bromoacetyl)benzofuran (II) was suspended in 750 ml. MeOH and cooled to 0.degree., 9.1 g. NaBH4 added at 10-20.degree., and the mixt. stirred 1 hr. at room temp. to give

1-(2-benzofuryl)-1-hydroxy-2-bromoethane. The Cl analog of II gave I (R = Cl) (III). III (16 g.) and 17.5 g. iso-PrNH2 in 84 ml. EtOH was refluxed 24 hrs. to give 9.2 g. I (R = isopropylamino), m. 108-9.degree.. Similarly prepd. were the following I (R and m.p. given): ethylamino, 108.degree.; phenethylamino, 99-100.degree.; allylamino, 92.degree.; cyclohexylamino, 106.degree.; .beta.-(3,4-methylenedioxyphenyl)ethylamino, -- (HCl salt m. 184.degree.); .alpha.-methylphenethylamino, -- (HCl salt m. 145.degree.); 1-methyl-3-phenyl-propylamino, -- (HCl salt m. 171.degree.); 3-phenylpropylamino, 110.degree.; butylamino, -- (HCl salt m. 172.3.degree.); tert-butylamino, 133.degree.; phenoxyethylamino, -- (HCl salt m. 202.degree.). The products depress the cardiac contraction provoked by noradrenaline or aleudrine.

IT **5536-81-2**, 2-Benzofuranmethanol, .alpha.-[[(2-phenoxyethyl)amino]methyl]- **5536-82-3**, 2-Benzofuranmethanol, .alpha.-[[(2-phenoxyethyl)amino]methyl]-, hydrochloride **5536-84-5**, 2-Benzofuranmethanol, .alpha.-[[(3-phenylpropyl)amino]methyl]- **5536-85-6**, 2-Benzofuranmethanol, .alpha.-[[(1-methyl-3-phenylpropyl)amino]methyl]-, hydrochloride **5536-86-7**, 2-Benzofuranmethanol, .alpha.-[[(.alpha.-methylphenethyl)amino]methyl]-, hydrochloride **5536-89-0**, 2-Benzofuranmethanol, .alpha.-[(phenethylamino)methyl]-
(prepn. of)

L119 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2002 ACS
AN 1966:93335 HCAPLUS
DN 64:93335
OREF 64:17543a-c
TI 2-(2-Amino-1-hydroxyethyl)benzofurans
PA Societe Belge de l'Azote et des Produits Chimiques du Marly, S.A.
SO 12 pp.
DT Patent
LA Unavailable
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI BE 663926		19651116	BE	19650514

GI For diagram(s), see printed CA Issue.

AB Compds. of the general formula I are prepd. and can be used as hypotensive agents. Thus, 30 g. 2-bromoacetylbenzofuran in 750 ml. MeOH is treated overnight with 9.1 g. NaBH4 to give 76% 1-(2-benzofuryl)-1-hydroxy-2-bromoethane. Similarly prepd. is 1-(2-benzofuryl)-1-hydroxy-2-chloroethane (II). A mixt. of 16 g. II, 17.5 g. iso-PrNH2, and 84 ml. EtOH is refluxed 24 hrs. to give 61% 1-(2-benzofuryl)-1-hydroxy-2-isopropylaminoethane (III), m. 108-9.degree. (cyclohexane), CHl salt m. 155.degree. (MeEtCO-EtOH). Similarly prepd. are the following I (R, m.p., m.p. HCl salt, and % yield given): Et, 108.degree. (cyclohexane), --, 43.3; PhCH2CH2, 99-100.degree. (cyclohexane), --, 30.1; allyl, 92.degree. (ligroine), --, 25.7; cyclohexyl, 106.degree. (cyclohexane), --, 17.2; 2-(3,4-methylenedioxyphenyl)ethyl, --, 184.degree. (MeEtCO-EtOH), --; PhCH2-CHMe, --, 145.degree., (MeEtCO), 23; PhCH2CH2CHMe, --, 171.degree. (tetrahydrofuran), --; Ph(CH2)3, 110.degree. (cyclohexane), --, 24; Bu, --, 172-3.degree. (EtOH-MeEtCO), 42; tert-Bu, 133.degree. (cyclohexane), --, 21.4; PhOCH2CH2, --, 202.degree. (EtOH), 37.9. A tablet or pill is prepd. from 25 ml. III.HCl, 161 ml. lactose, 4 ml. gelatin, 50 ml. potato starch, 1.5 ml. talc, and 2.5 ml. Mg stearate.

IT **5536-81-2**, 2-Benzofuranmethanol, .alpha.-[[(2-phenoxyethyl)amino]methyl]- **5536-82-3**, 2-Benzofuranmethanol, .alpha.-[[(2-phenoxyethyl)amino]methyl]-, hydrochloride **5536-84-5**, 2-Benzofuranmethanol, .alpha.-[[(3-phenylpropyl)amino]methyl]- **5536-85-6**, 2-Benzofuranmethanol, .alpha.-[[(1-methyl-3-phenylpropyl)amino]methyl]-, hydrochloride **5536-86-7**, 2-Benzofuranmethanol, .alpha.-[[(.alpha.-methylphenethyl)amino]methyl]-, hydrochloride **5536-89-0**, 2-Benzofuranmethanol,

.alpha.-[(phenethylamino)methyl]-
(prepn. of)

=> fil reg
FILE 'REGISTRY' ENTERED AT 10:44:32 ON 13 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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provided by InfoChem.

STRUCTURE FILE UPDATES: 11 OCT 2002 HIGHEST RN 460983-61-3
DICTIONARY FILE UPDATES: 11 OCT 2002 HIGHEST RN 460983-61-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

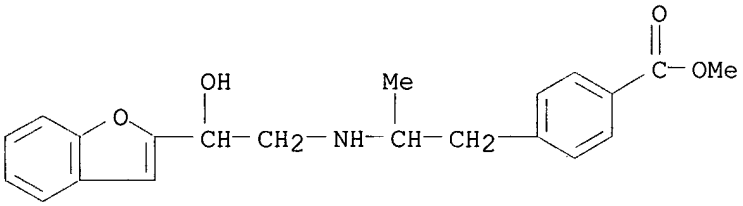
Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP
PROPERTIES for more information. See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

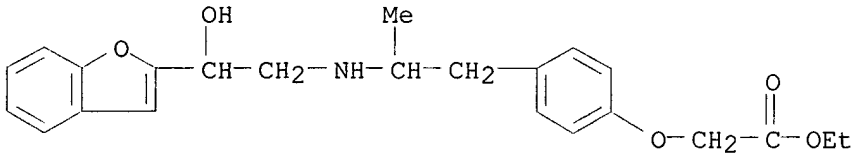
=> d l111 ide can 1 10 20 30 40 50 60 70 73

L111 ANSWER 1 OF 73 REGISTRY COPYRIGHT 2002 ACS
RN 345585-05-9 REGISTRY
CN Benzoic acid, 4-[2-[[2-(2-benzofuranyl)-2-hydroxyethyl]amino]propyl]-,
methyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C21 H23 N O4
SR CA



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L111 ANSWER 10 OF 73 REGISTRY COPYRIGHT 2002 ACS
RN 102198-54-9 REGISTRY
CN Acetic acid, [4-[2-[[2-(2-benzofuranyl)-2-hydroxyethyl]amino]propyl]phenox
y]-, ethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C23 H27 N O5
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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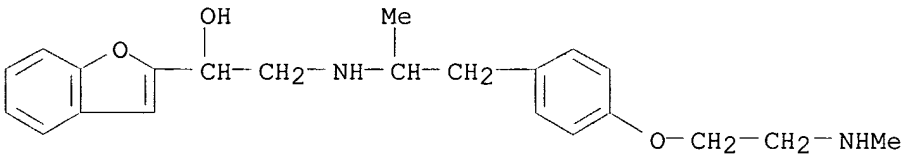
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 104:224720

L111 ANSWER 20 OF 73 REGISTRY COPYRIGHT 2002 ACS
RN 86608-16-4 REGISTRY
CN 2-Benzofuranmethanol, .alpha.-[[[1-methyl-2-[4-[2-(methylamino)ethoxy]phenyl]ethyl]amino]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)
MF C22 H28 N2 O3 . 2 Cl H
LC STN Files: CA, CAPLUS
CRN (86608-15-3)



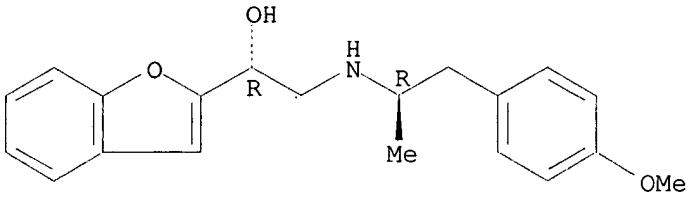
●2 HCl

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 99:194608

L111 ANSWER 30 OF 73 REGISTRY COPYRIGHT 2002 ACS
RN 83123-45-9 REGISTRY
CN 2-Benzofuranmethanol, .alpha.-[[[2-(4-methoxyphenyl)-1-methylethyl]amino]methyl]-, (R*,R*)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Benzofuranmethanol, .alpha.-[[[2-(4-methoxyphenyl)-1-methylethyl]amino]methyl]-, (R*,R*)-(.+-.)-
FS STEREOSEARCH
MF C20 H23 N O3
LC STN Files: CA, CAPLUS, USPATFULL

Relative stereochemistry.

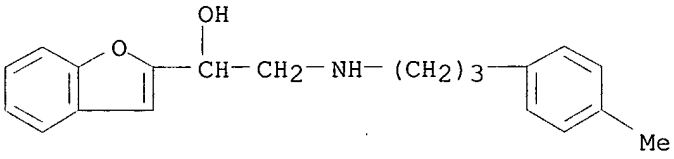


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 97:144754

L111 ANSWER 40 OF 73 REGISTRY COPYRIGHT 2002 ACS
RN 83123-35-7 REGISTRY
CN 2-Benzofuranmethanol, .alpha.-[[[3-(4-methylphenyl)propyl]amino]methyl]-
(9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C20 H23 N O2
LC STN Files: CA, CAPLUS, USPATFULL



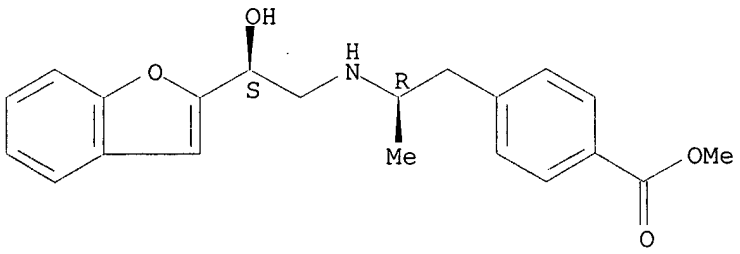
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 97:144754

L111 ANSWER 50 OF 73 REGISTRY COPYRIGHT 2002 ACS
RN 79390-98-0 REGISTRY
CN Benzoic acid, 4-[2-[[2-(2-benzofuranyl)-2-hydroxyethyl]amino]propyl]-,
methyl ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H23 N O4
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



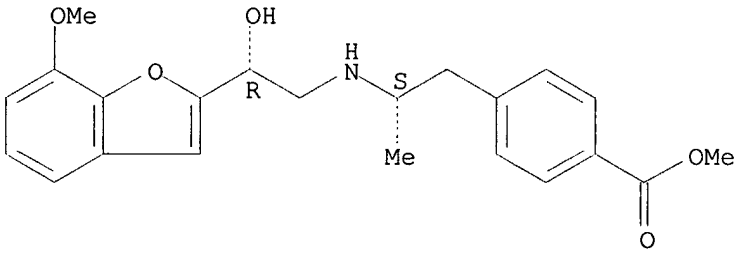
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 95:168976

L111 ANSWER 60 OF 73 REGISTRY COPYRIGHT 2002 ACS
RN 79362-76-8 REGISTRY
CN Benzoic acid, 4-[2-[[2-hydroxy-2-(7-methoxy-2-benzofuranyl)ethyl]amino]propyl]-, methyl ester, (R*,S*)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H25 N O5
LC STN Files: CA, CAPLUS, USPATFULL

Relative stereochemistry.

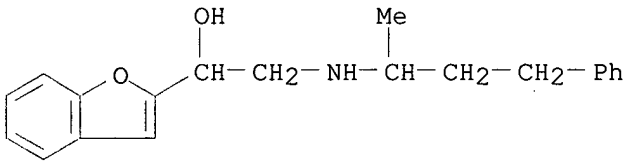


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 95:168976

L111 ANSWER 70 OF 73 REGISTRY COPYRIGHT 2002 ACS
RN 5536-85-6 REGISTRY
CN 2-Benzofuranmethanol, .alpha.-[[(1-methyl-3-phenylpropyl)amino]methyl]-, hydrochloride (7CI, 8CI) (CA INDEX NAME)
MF C20 H23 N O2 . Cl H
LC STN Files: CA, CAOLD, CAPLUS



HCl

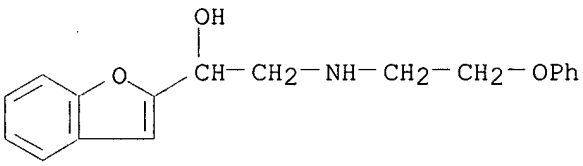
3 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES IN FILE CAPLUS (1962 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 65:56683

REFERENCE 2: 64:104078

REFERENCE 3: 64:93335

L111 ANSWER 73 OF 73 REGISTRY COPYRIGHT 2002 ACS
RN 5536-81-2 REGISTRY
CN 2-Benzofuranmethanol, .alpha.-[[(2-phenoxyethyl)amino]methyl]- (8CI) (CA INDEX NAME)
FS 3D CONCORD
MF C18 H19 N O3
CI COM
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 64:104078

REFERENCE 2: 64:93335

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SET COST OFF

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E SOUBRIE P/AU
L2 215 S E3-E8
E SANOFI/PA,CS
L3 1921 S E2,E3,E4
L4 1921 S SANOFI?/PA,CS
E SYNTHELABO/PA,CS
L5 2057 S SYNTHELAB?/PA,CS
L6 97 S L1,L2 AND L3-L5
E FR97-870/PA,CS
E FR97-870/AP,PRN
L7 1 S E3,E4
E WO98-FR154/AP,PRN
L8 1 S E3,E4
E US6344474/PN
L9 1 S E3
L10 1 S L1-L6 AND L7-L9
SEL RN

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L11            1 S E1
L12            7 S 168273-06-1/CRN
L13              STR
L14            5 S L13
L15              STR L13
L16          103 S L15 FUL
                 SAV L16 JKIM44531/A
L17           95 S L16 NOT L11,L12

     FILE 'HCAOLD' ENTERED AT 09:20:53 ON 13 OCT 2002
L18            0 S L11 OR L12 OR L17

     FILE 'HCAPLUS' ENTERED AT 09:20:59 ON 13 OCT 2002
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L20          119 S RIMONABANT OR SR141716 OR SR()(141716 OR 141 716)
L21          608 S SR141716# OR SR()(141716# OR 141 716#)
L22          618 S L19-L21
L23           25 S L17
L24          622 S L22,L23
L25           58 S L11
L26          119 S SR141716 OR SR()(141716 OR 141 716)
L27          130 S L25,L26
L28          492 S L24 NOT L27
L29          362 S L1,L2 NOT L10

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     FILE 'HCAPLUS' ENTERED AT 09:25:08 ON 13 OCT 2002
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L30          SEL L29 1- RN :     558 TERMS
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L32            1 S L31 AND (46.150.18 AND 591.49.51)/RID
                 E C22H26CLNO4/MF
L33            7 S E3 AND (46.150.18 AND 591.49.51)/RID
L34            1 S L33 AND 2S
L35            1 S L33 AND 2R
L36            1 S L34 AND L35
                 SEL RN
L37            1 S E1/CRN
L38            1 S L32,L37
L39            7 S L32-L37 NOT L38
                 SEL RN
L40            7 S E3-E8/CRN NOT L38
L41            2 S L36,L38
L42           13 S L33,L40 NOT L41

     FILE 'HCAPLUS' ENTERED AT 09:31:30 ON 13 OCT 2002
L43           59 S L41
L44           70 S SR58611 OR SR58611A OR SR()(58611 OR 58611A OR 58 611 OR 58 6
L45           78 S L43,L44
L46           10 S L42
L47           82 S L45,L46
L48           44 S L27 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L49          164 S L28 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L50            0 S L48 AND L49
L51          170 S L12
L52            6 S L28,L51 AND L27
L53            4 S L52 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L54           80 S L51 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
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L55          44 S L48,L53
L56          44 S L55 AND L1-L10,L19-L29,L48-L55
L57          46 S L11(L)(THU OR BAC)/RL
L58         146 S (L12 OR L17)(L)(THU OR BAC)/RL
L59          24 S L56 AND L57,L58
L60           4 S L55 AND 63/SC
L61           0 S L55 AND 63/SX
L62          36 S L55 AND 1/SC,SX
L63          24 S L59,L60
L64          16 S L62 NOT L63
                SEL DN AN 7
L65           1 S E9-E11 AND L64
L66          25 S L63,L65 AND L1-L10,L19-L29,L48-L65

     FILE 'REGISTRY' ENTERED AT 09:39:54 ON 13 OCT 2002

     FILE 'HCAPLUS' ENTERED AT 09:40:14 ON 13 OCT 2002

     FILE 'REGISTRY' ENTERED AT 09:41:29 ON 13 OCT 2002

     FILE 'REGISTRY' ENTERED AT 09:42:09 ON 13 OCT 2002

     FILE 'HCAPLUS' ENTERED AT 09:43:37 ON 13 OCT 2002
L67          39 S L41 (L) (THU OR BAC)/RL
L68           9 S L47 AND 63/SC,SX
L69          51 S L47 AND 1/SC,SX
L70          60 S L47 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L71          44 S L67-L69 AND L70

     FILE 'REGISTRY' ENTERED AT 09:45:36 ON 13 OCT 2002
L72             STR
L73           2 S L72 SAM
L74             STR L72
L75           9 S L74
L76             STR L74
L77           3 S L76
L78             STR L76
L79           0 S L78
L80             STR L74
L81           7 S L80
L82             SCR 2043 OR 2127
L83           7 S L80 NOT L82
L84           3 S L78 NOT L82
                SAV L78 JKIM44531A/Q
L85             STR
L86          18 S L85
L87         375 S L85 FUL
                SAV L87 JKIM44531B/A
L88             STR L85
L89          10 S L88 SAM SUB=L87
L90         237 S L88 FUL SUB=L87
                SAV L90 JKIM44531C/A
L91         138 S L87 NOT L90
L92          57 S L91 AND C6-C6/ES AND 46.150.18/RID
L93          76 S L88 CSS FUL SUB=L90
                SAV L93 JKIM44531D/A
L94         161 S L90 NOT L93
L95          61 S L93 NOT L41,L42

     FILE 'HCAPLUS' ENTERED AT 10:12:57 ON 13 OCT 2002
L96          18 S L95
L97          18 S L96 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L98          13 S L97 AND L71
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L99          49 S L71,L97,L98

     FILE 'REGISTRY' ENTERED AT 10:14:11 ON 13 OCT 2002

     FILE 'HCAPLUS' ENTERED AT 10:14:26 ON 13 OCT 2002

     FILE 'REGISTRY' ENTERED AT 10:14:49 ON 13 OCT 2002

     FILE 'REGISTRY' ENTERED AT 10:15:56 ON 13 OCT 2002
L100            STR L78
L101          3 S L100
L102         75 S L100 FUL
                SAV L102 JKIM44531E/A
L103            STR L100
L104         17 S L103
L105       4534 S L103 FUL
                SAV L105 JKIM44531F/A
L106            STR L103
L107       4607 S L102 OR L105
L108         50 S L106 CSS SAM SUB=L107
L109       2224 S L106 CSS FUL SUB=L107
                SAV L109 JKIM44531G/A
L110          2 S L102 AND L109
L111         73 S L102 NOT L110

     FILE 'HCAPLUS' ENTERED AT 10:35:48 ON 13 OCT 2002
L112         10 S L111
L113         10 S L112 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L114          5 S L113 AND (1 OR 63)/SC,SX
L115          3 S L111 (L) (THU OR BAC)/RL
L116          6 S L114,L115
L117          4 S L112 NOT L116
                SEL DN AN 2
L118          3 S L117 NOT E12-E14
L119          9 S L116,L118

     FILE 'REGISTRY' ENTERED AT 10:39:26 ON 13 OCT 2002
L120       2222 S L109 NOT L110
L121       2312 S L105 NOT L120

     FILE 'HCAPLUS' ENTERED AT 10:40:08 ON 13 OCT 2002
L122        508 S L120
L123       2818 S L121
L124         78 S L120(L)THU/RL
L125        666 S L121 (L) THU/RL
L126        324 S L122,L123 AND 63/SC
L127        505 S L124-L126 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L128       1213 S BETA 3 (L) ADRENOCEPTOR
L129        886 S BETA 3 (L) ADRENERGIC (L) RECEPTOR
L130         24 S L127 AND L128,L129

     FILE 'REGISTRY' ENTERED AT 10:42:57 ON 13 OCT 2002

     FILE 'HCAPLUS' ENTERED AT 10:43:18 ON 13 OCT 2002
L131          9 S  L119 NOT L130

     FILE 'REGISTRY' ENTERED AT 10:44:32 ON 13 OCT 2002
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FILE 'REGISTRY' ENTERED AT 11:07:24 ON 13 OCT 2002
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provided by InfoChem.

STRUCTURE FILE UPDATES:   11 OCT 2002  HIGHEST RN 460983-61-3
DICTIONARY FILE UPDATES:  11 OCT 2002  HIGHEST RN 460983-61-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sta que l19
L6              STR
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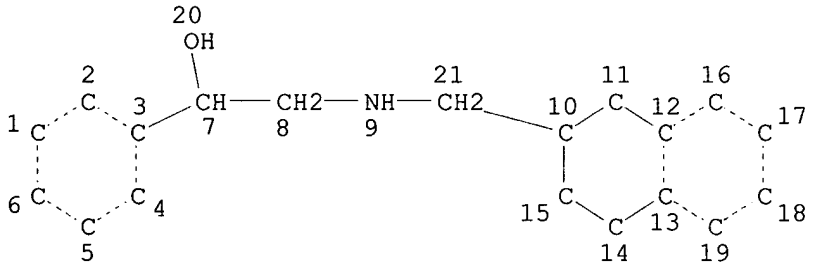

Structure for Formula V

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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC  10
NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE
L8          240 SEA FILE=REGISTRY SSS FUL L6
L16             STR
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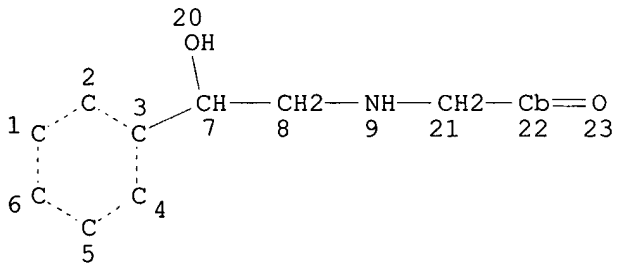


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
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GGCAT   IS PCY  AT  22
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  13

STEREO ATTRIBUTES: NONE
L18         196 SEA FILE=REGISTRY SUB=L8 SSS FUL L16
L19          44 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 NOT L18


=> d his l19-

     (FILE 'REGISTRY' ENTERED AT 11:04:08 ON 13 OCT 2002)
                SAV L18 JKIM44531I/A
L19          44 S L8 NOT L18

     FILE 'HCAPLUS' ENTERED AT 11:06:29 ON 13 OCT 2002
L20          11 S L19
L21           7 S L20 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L22          10 S L19 (L) (THU OR BAC)/RL
L23          10 S L20  AND (1 OR 63)/SC,SX
L24           7 S L21 AND L22,L23

     FILE 'REGISTRY' ENTERED AT 11:07:24 ON 13 OCT 2002

=> fil hcaplus
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FILE COVERS 1907 - 13 Oct 2002  VOL 137 ISS 16
FILE LAST UPDATED: 11 Oct 2002  (20021011/ED)

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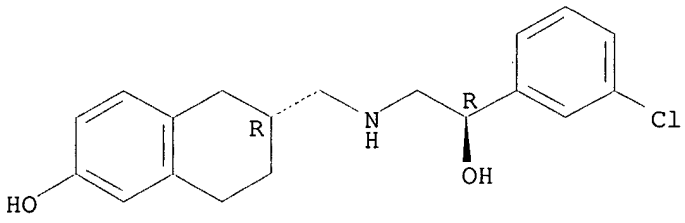
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

=> d l24 bib abs hitrn fhitstr retable tot

L24  ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 2002 ACS
AN   1998:546795  HCAPLUS
DN   129:254774
TI   In vitro inhibition of human colonic motility with SR 59119A and SR
     59104A: evidence of a .beta.3-adrenoceptor-mediated effect
AU   Bardou, Marc; Dousset, Bertrand; Deneux-Tharaux, Catherine; Smadja,
```

Claude; Naline, Emmanuel; Chaput, Jean-Claude; Naveau, Sylvie; Manara, Luciano; Croci, Tiziano; Advenier, Charles
CS Departement de Pharmnacologie, Faculte de Medecine Paris-Ouest, Paris, F-75270, Fr.
SO European Journal of Pharmacology (**1998**), 353(2/3), 281-287
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB The new .beta.3-adrenoceptor is present in the gastrointestinal tract of various species. This study aimed to show that this receptor modulates human colonic motility in vitro. The authors used circular muscle strips from the human colon suspended in single organ baths contg. Krebs soln. and subjected to an initial 1.5-2 g tension. The authors measured the effects of different .beta.3-adrenoceptor agonists, including SR 59104A (N-[(6-hydroxy-1,2,3,4-tetrahydronaphthalen-(2R)-2-yl)methyl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine hydrochloride), SR 59119A (N-[(7-methoxy-1,2,3,4-tetrahydronaphthalen-(2R)-2-yl)methyl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine hydrochloride), BRL 37344 [(R,R + S,S) [4-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]phenoxy]acetic acid], and of isoprenaline and salbutamol in the absence or in the presence of propranolol alone or in combination with the .beta.3-adrenoceptor antagonist SR 59230A (3-(2-ethylphenoxy)-1-[(1S)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-(2S)-2-propanol oxalate) on amplitude of spontaneous contractions. To evaluate a possible .beta.2-adrenoceptor-mediated effect, the authors studied the action of these compds. on human isolated bronchi. On the human isolated colon, SR 59119A, SR 59104A and isoprenaline reduced the initial amplitude of spontaneous contractions by 60%. The curves obtained in the presence of antagonists suggested an action mediated by .beta.3-adrenoceptor stimulation, since propranolol did not antagonize the action of SR 59119A and SR 59104A, whereas the combination of propranolol and SR 59230A significantly displaced the concn.-response curve of these agonists to the right. This study provides pharmacol. evidence of modulation of human colonic motility, and esp. of the amplitude of spontaneous contractions, by the atypical 3-adrenoceptor, the .beta.3-adrenoceptor.
IT **136758-90-2**, SR 59104A **136758-99-1**, SR 59119A
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(in vitro inhibition of human colonic motility with SR 59119A and SR 59104A and evidence of a .beta.3-adrenoceptor-mediated effect)
IT **136758-90-2**, SR 59104A
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(in vitro inhibition of human colonic motility with SR 59119A and SR 59104A and evidence of a .beta.3-adrenoceptor-mediated effect)
RN 136758-90-2 HCAPLUS
CN 2-Naphthalenol, 6-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-, hydrochloride, (6R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L24 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:509094 HCAPLUS
DN 129:144879
TI Use of agonists of beta-3 adrenergic receptors for preparing wound-healing medicines
IN Bernat, Andre; Herbert, Jean-Marc; Arnone, Michele
PA Sanofi, Fr.
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

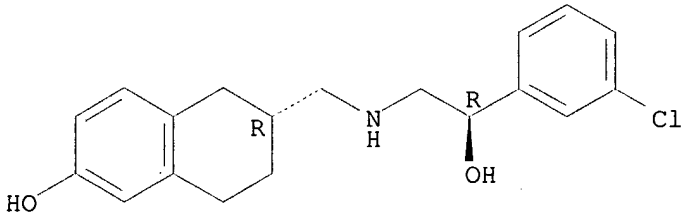
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9831357	A1	19980723	WO 1998-FR105	19980121 <--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	FR 2758460	A1	19980724	FR 1997-584	19970121 <--
	FR 2758460	B1	19991231		
	ZA 9800484	A	19980730	ZA 1998-484	19980121 <--
	AU 9859941	A1	19980807	AU 1998-59941	19980121 <--
	EP 966276	A1	19991229	EP 1998-903099	19980121 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	BR 9807288	A	20000321	BR 1998-7288	19980121 <--
	JP 2001508790	T2	20010703	JP 1998-533861	19980121 <--
	US 6235793	B1	20010522	US 1999-341656	19990715 <--
	NO 9903548	A	19990720	NO 1999-3548	19990720 <--
PRAI	FR 1997-584	A	19970121 <--		
	WO 1998-FR105	W	19980121 <--		

OS MARPAT 129:144879
AB Agonists of beta-3 adrenergic receptors (Markush structure given) are used for prepg. wound-healing medicines (no data).
IT **210757-90-7 210757-91-8**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(use of agonists of beta-3 adrenergic receptors for prepg. wound-healing medicines)
IT **210757-90-7**
RL: **BAC (Biological activity or effector, except adverse)**; BSU

(Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(use of agonists of beta-3 adrenergic receptors for prepg. wound-healing medicines)

RN 210757-90-7 HCAPLUS
CN 2-Naphthalenol, 6-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-, (6R)- (9CI) (CA INDEX NAME)

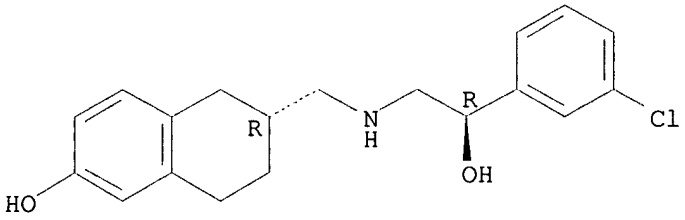
Absolute stereochemistry.



L24 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:306016 HCAPLUS
DN 129:76216
TI Influence of .beta.-adrenoceptor agonists on the pulmonary circulation. Effects of a .beta.3-adrenoceptor antagonist, SR 59230A
AU Dumas, Monique; Dumas, Jean-Paul; Bardou, Marc; Rochette, Luc; Advenier, Charles; Giudicelli, Jean-Francois
CS Laboratoire de Physiopathologie et de Pharmacologie Cardiovasculaires Experimentales, Faculte de Medecine, Dijon, 21000, Fr.
SO European Journal of Pharmacology (**1998**), 348(2/3), 223-228
CODEN: EJPHAZ; ISSN: 0014-2999
PB Elsevier Science B.V.
DT Journal
LA English
AB The aims of this study were (a) to compare in the rat isolated perfused lung prepn., the effects of isoprenaline and of three .beta.3-adrenoceptors agonists, SR 59104A, [N-[[6-hydroxy-1,2,3,4-tetrahydronaphthalen-(2R)-2yl]methyl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine-HCl], SR 59119A [N-[[7-methoxy-1,2,3,4-tetrahydronaphtalen-(2R)-2yl]methyl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine-HCl] and SR 58611A [ethyl [(7S)-7-[(2R)-2-(3-chlorophenyl)-2-hydroxyethylamino]-5,6,7,8-tetrahydronaphthalen-2-yloxy]acetate-HCl] on hypoxia-induced pulmonary vasoconstriction, and (b) to investigate the potential existence of atypical .beta.-adrenoceptors in these effects. Propranolol (0.1 .mu.M) was used to antagonize .beta.1- and .beta.2-adrenoceptors whereas SR 59230A, 3-(2-ethylphenoxy)-1-[(1S)-1,2,3,4-tetrahydronapht-1-ylamino]-(2S)-2-propanol oxalate) (0.3 .mu.M) was used to block .beta.3-adrenoceptors. Isoprenaline and the three .beta.3-adrenoceptors agonists caused concn.-dependent relaxations during the pulmonary pressure response. Propranolol and SR 59230A inhibited the relaxant effects of isoprenaline. SR 59230A but not propranolol inhibited those of SR 59104A. Finally, propranolol and SR 59230A failed to oppose SR 59119A- and SR 58611A-induced relaxant effects. In concns. .gtoreq.1 .mu.M, SR 59230A caused per se a relaxation of the hypoxic vasoconstricted lung. These results suggest the existence of atypical .beta.-adrenoceptors in the rat pulmonary vessels.
IT **136758-90-2**, SR 59104A **136758-99-1**, SR 59119A
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-adrenoceptor agonists and .beta.3-adrenoceptor antagonist SR 59230A effect on pulmonary circulation)
IT **136758-90-2**, SR 59104A

RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-adrenoceptor agonists and .beta.3-adrenoceptor antagonist SR 59230A effect on pulmonary circulation)
RN 136758-90-2 HCAPLUS
CN 2-Naphthalenol, 6-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-, hydrochloride, (6R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

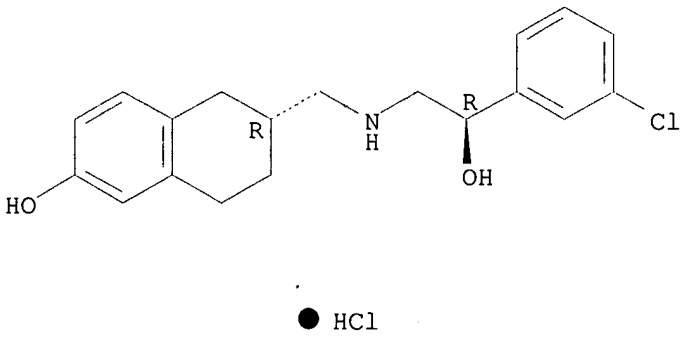
L24 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:93789 HCAPLUS
DN 126:99317
TI Use of beta3-adrenergic agonists for inducing the release of glucagon-like-peptide
IN Bouloux, Cyril Jacques; Manara, Luciano; Bloom, Stephen Robert
PA Sanofi, Fr.
SO Fr. Demande, 9 pp.
CODEN: FRXXBL
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	FR 2732894	A1	19961018		FR 1995-4448	19950413	<--
	FR 2732894	B1	19970704				
	FR 2734482	A1	19961129		FR 1995-12694	19951027	<--
	FR 2734482	B1	19970814				
	BE 1009698	A3	19970701		BE 1996-294	19960409	<--
	IT 1298492	B1	20000110		IT 1996-TO284	19960412	<--
PRAI	FR 1995-4448	A	19950413	<--			
	FR 1995-12694	A	19951027	<--			

AB Beta3-adrenergic agonists are useful for inducing the release of glucagon-like-peptide. These agonists are administered at 0.01-30 mg/kg body wt. in different dosage forms (no data).
IT **136758-90-2 136758-99-1**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(beta3-adrenergic agonists for inducing release of glucagon-like-peptide)
IT **136758-90-2**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(beta3-adrenergic agonists for inducing release of glucagon-like-peptide)
RN 136758-90-2 HCAPLUS

CN 2-Naphthalenol, 6-[[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-, hydrochloride, (6R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

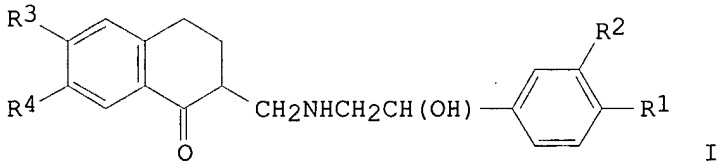


● HCl

L24 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:530933 HCAPLUS
DN 117:130933
TI Preparation of [[[(oxotetrahydronaphthyl)methyl]amino]ethyl]benzenes as antihypertensives
IN McDermed, John Dale; Hurley, Kevin Patrick; Tadepalli, Anjaneyulu Seetharam; Chang, Vincent Huech Tien
PA Wellcome Foundation Ltd., UK
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9205143	A1	19920402	WO 1991-GB1602	19910919 <--
	W: JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
	EP 549668	A1	19930707	EP 1991-916818	19910919 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 06501250	T2	19940210	JP 1991-515271	19910919 <--
	US 5405872	A	19950411	US 1993-30018	19930322 <--
PRAI	GB 1990-20695		19900922 <--		
	WO 1991-GB1602		19910919 <--		

OS MARPAT 117:130933
GI



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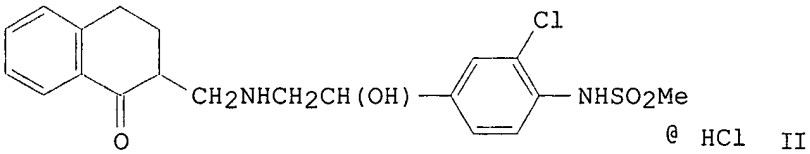


@ HCl II

AB Title compds. [I; R1 = H, OH, alkyl, halo, carbamoyl, aminosulfonyl(amino), etc.; R2 = H, OH, halo, alkoxycarbonyl, aminosulfonyl, alkylsulfonylamino; R3 = H, OH, alkoxy; R4 = H, alkoxy, halo, NO2] were prepd. Thus, 2'-chloro-5'-[(1-hydroxy-2-amino)ethyl]methanesulfonanilide hydrochloride (prepn. from 4-chloro-3-nitroacetophenone given) and N-(1,2,3,4-tetrahydro-1-oxo-2-naphthyl)methyl-N,N,N-trimethylammonium iodide (prepn. given) were stirred in MeCN contg. Et3N to give title compd. II as a mixt. of 2 pairs of diastereomers. II at 10 mg/kg orally in rats gave a 46/53% redn. in systolic/diastolic blood pressure.

IT **142951-68-6P**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as antihypertensive)

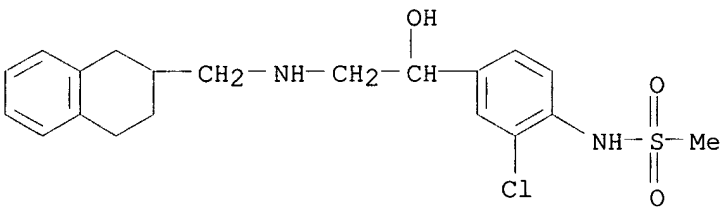
IT **142951-68-6P**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as antihypertensive)

RN 142951-68-6 HCAPLUS

CN Methanesulfonamide, N-[2-chloro-4-[1-hydroxy-2-[[(1,2,3,4-tetrahydro-2-naphthalenyl)methyl]amino]ethyl]phenyl]-, mono(methanesulfonate) (salt) (9CI) (CA INDEX NAME)

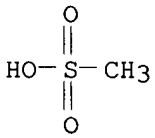
CM 1

CRN 142951-67-5
CMF C20 H25 Cl N2 O3 S



CM 2

CRN 75-75-2
CMF C H4 O3 S



L24 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2002 ACS
AN 1991:607684 HCAPLUS
DN 115:207684
TI Phenylethanolaminomethyltetralins, their preparation, and pharmaceuticals containing them for treatment of intestinal disorders and glaucoma

IN Cecchi, Roberto; Guzzi, Umberto
PA SANOFI, Fr.; Midy S.p.A.
SO Eur. Pat. Appl., 45 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	EP 436435	A1	19910710	EP 1990-403762	19901226	<--
	EP 436435	B1	19940323			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE					
	FR 2656607	A1	19910705	FR 1989-17465	19891229	<--
	FR 2656607	B1	19940311			
	AT 103269	E	19940415	AT 1990-403762	19901226	<--
	ES 2054304	T3	19940801	ES 1990-403762	19901226	<--
	CA 2033243	AA	19910630	CA 1990-2033243	19901227	<--
	CA 2033243	C	19980707			
	JP 04210663	A2	19920731	JP 1990-418873	19901227	<--
	JP 2521191	B2	19960731			
	US 5130339	A	19920714	US 1990-635950	19901228	<--
PRAI	FR 1989-17465		19891229	<--		
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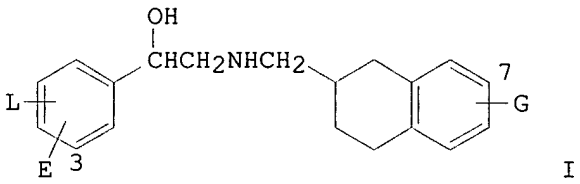
OS MARPAT 115:207684
GI



I

AB Title compds. I [E = H, alkyl, alkoxy, Ph, NO2, halo, CF3; L = H, alkyl, Ph, alkoxy, NO2, halo; or EL = CH:CHCH:CH, (CH2)4; G = H, Cl, OH, OG', G' = alkyl (optionally substituted by OH, alkoxy, alkoxycarbonyl, CO2H, or cycloalkyl), cycloalkyl, alkanoyl] and salts were prepd. as selective modulators of intestinal motility, and for treatment of ocular hypertension and glaucoma (no data). For example, amidation of 3-chloromandelic acid with 2-(aminomethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene and redn. of the amide with BH3.Me2S in THF, followed by acidification, gave I.HCl (E = 3-Cl, L = H, G = 7-OMe) (II). The EC50 of II for inhibition of spontaneous contraction of isolated rat colon and uterus, resp., were 43 and 2453 nM, vs. 194 and 350 nM for the known analog bearing a 7-OEt group and lacking the naphthylmethyl CH2 unit. Five formulations, 33 syntheses of I, and 22 precursor syntheses are described.

IT **136759-09-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of drugs)

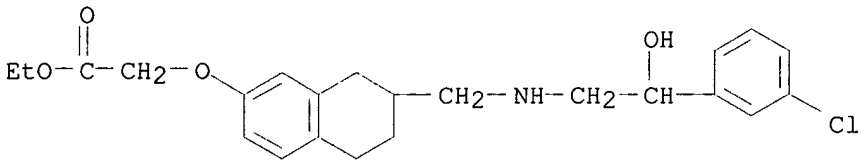
IT **136758-71-9P 136758-72-0P 136758-73-1P**
136758-74-2P 136758-75-3P 136758-76-4P
136758-77-5P 136758-78-6P 136758-79-7P
136758-80-0P 136758-81-1P 136758-82-2P
136758-83-3P 136758-84-4P 136758-85-5P
136758-86-6P 136758-87-7P 136758-88-8P
136758-89-9P 136758-90-2P 136758-91-3P

136758-92-4P 136758-94-6P 136758-96-8P
136758-97-9P 136758-98-0P 136758-99-1P
136759-00-7P 136759-01-8P 136759-02-9P
136759-03-0P 136759-04-1P 136759-05-2P
136759-06-3P 136759-07-4P 136759-08-5P
136759-09-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for treatment of intestinal disorders and glaucoma)

IT **136759-09-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of drugs)

RN 136759-09-6 HCAPLUS

CN Acetic acid, [[7-[[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester (9CI) (CA INDEX NAME)



L24 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2002 ACS

AN 1990:526611 HCAPLUS

DN 113:126611

TI Preparation of antihypertensive sulfonanilides

IN McDermed, John Dale; Tadepalli, Anjaneyulu Seetharm; Chang, Vincent Huech Tien; Hurley, Kevin Patrick; Freeman, Harold Stanley

PA Wellcome Foundation Ltd., UK

SO Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	EP 338793	A2	19891025	EP 1989-303862	19890419	<--
	EP 338793	A3	19910102			
	EP 338793	B1	19931027			
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	FI 8901866	A	19891021	FI 1989-1866	19890419	<--
	FI 91398	B	19940315			
	FI 91398	C	19940627			
	NO 8901609	A	19891023	NO 1989-1609	19890419	<--
	NO 173010	B	19930705			
	NO 173010	C	19931013			
	AU 8933221	A1	19891026	AU 1989-33221	19890419	<--
	AU 626850	B2	19920813			
	JP 02006461	A2	19900110	JP 1989-97714	19890419	<--
	HU 51600	A2	19900528	HU 1989-1909	19890419	<--
	HU 204028	B	19911128			
	ZA 8902880	A	19901228	ZA 1989-2880	19890419	<--
	AT 96429	E	19931115	AT 1989-303862	19890419	<--
	CA 1332615	A1	19941018	CA 1989-597117	19890419	<--
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	US 5102914	A	19920407	US 1989-455909	19891218	<--

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PRAI	GB 1988-9314		19880420 <--		
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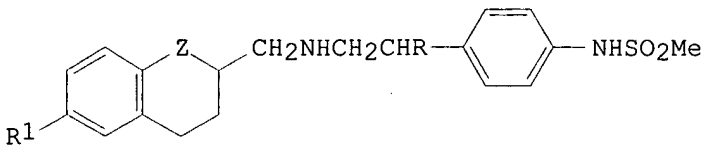
	US 1989-340226		19890419 <--		
	US 1989-340437		19890419 <--		
	US 1990-479181		19900212 <--		
	US 1990-577057		19900831 <--		
OS	MARPAT 113:126611				
GI					



I

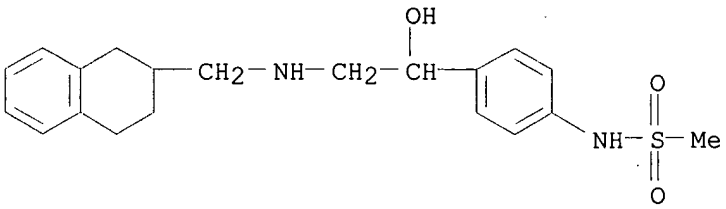
AB The sulfonanilides I (R = H, OH; R1 = H, alkoxy; Z = CO, CHOH, CH2) and I salts are prepd. as antihypertensives. 2-(4-Methanesulfonamidophenyl)ethy l methane sulfonate was added, at 100.degree., to a soln. of 2-aminomethyl-1,2,3,4-tetrahydronaphthalene and Et3N in DMF, to give I (R = R1 = H, Z = CH2) (II). Oral administration of 10 mg II/kg decreased the blood pressure of spontaneously hypertensive rats. Formulation examples are given.

IT **129280-12-2P**
RL: **BAC (Biological activity or effector, except adverse)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as antihypertensive)

IT **129280-12-2P**
RL: **BAC (Biological activity or effector, except adverse)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as antihypertensive)

RN 129280-12-2 HCAPLUS

CN Methanesulfonamide, N-[4-[1-hydroxy-2-[[(1,2,3,4-tetrahydro-2-naphthalenyl)methyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)



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FILE 'REGISTRY' ENTERED AT 11:07:43 ON 13 OCT 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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provided by InfoChem.

STRUCTURE FILE UPDATES: 11 OCT 2002 HIGHEST RN 460983-61-3
DICTIONARY FILE UPDATES: 11 OCT 2002 HIGHEST RN 460983-61-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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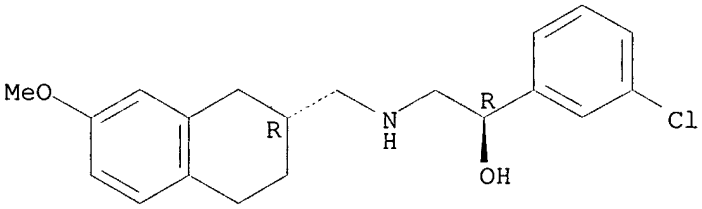
L25 ANSWER 1 OF 41 REGISTRY COPYRIGHT 2002 ACS
RN **210757-91-8** REGISTRY
CN Benzenemethanol, 3-chloro-.alpha.-[[[[(2R)-1,2,3,4-tetrahydro-7-methoxy-2-naphthalenyl]methyl]amino]methyl]-, (.alpha.R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C20 H24 Cl N O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



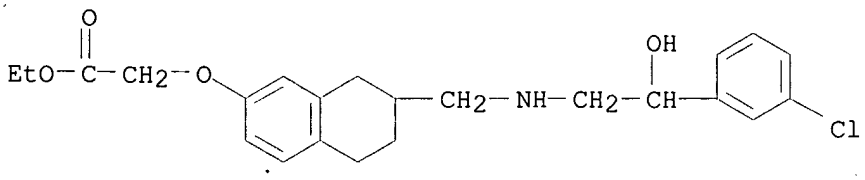
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 132:274338

REFERENCE 2: 129:144879

L25 ANSWER 4 OF 41 REGISTRY COPYRIGHT 2002 ACS
RN **136759-09-6** REGISTRY
CN Acetic acid, [[7-[[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C23 H28 Cl N O4
CI COM
SR CA
LC STN Files: CA, CAPLUS



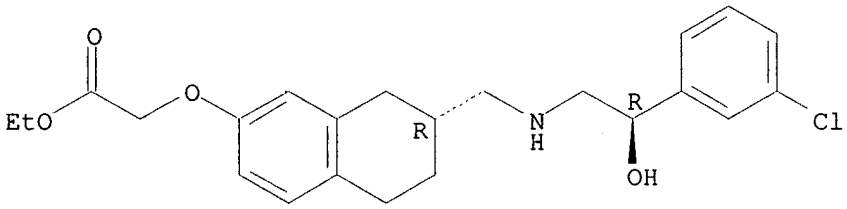
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 115:207684

L25 ANSWER 10 OF 41 REGISTRY COPYRIGHT 2002 ACS
RN **136759-03-0** REGISTRY
CN Acetic acid, [[7-[[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]oxy]-, ethyl ester, hydrochloride, [R-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H28 Cl N O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

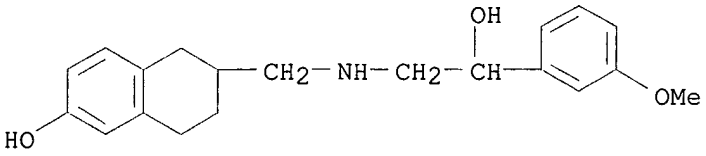


● HCl

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 115:207684

L25 ANSWER 15 OF 41 REGISTRY COPYRIGHT 2002 ACS
RN **136758-98-0** REGISTRY
CN 2-Naphthalenol, 5,6,7,8-tetrahydro-6-[[[2-hydroxy-2-(3-methoxyphenyl)ethyl]amino]methyl]-, hydrochloride (9CI) (CA INDEX NAME)
MF C20 H25 N O3 . Cl H
SR CA
LC STN Files: CA, CAPLUS



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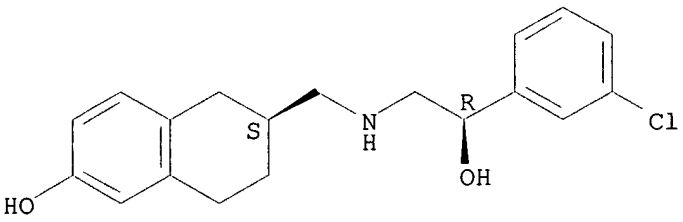
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 115:207684

L25 ANSWER 20 OF 41 REGISTRY COPYRIGHT 2002 ACS
RN **136758-91-3** REGISTRY
CN 2-Naphthalenol, 6-[[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-, hydrochloride, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H22 Cl N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



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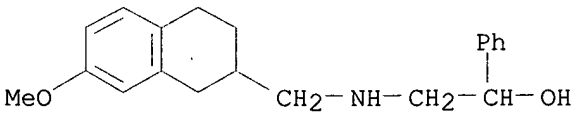
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 115:207684

L25 ANSWER 25 OF 41 REGISTRY COPYRIGHT 2002 ACS
RN **136758-86-6** REGISTRY
CN Benzenemethanol, .alpha.-[[[(1,2,3,4-tetrahydro-7-methoxy-2-naphthalenyl)methyl]amino]methyl]-, hydrochloride (9CI) (CA INDEX NAME)
MF C20 H25 N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS



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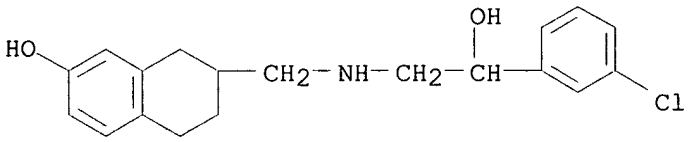
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 115:207684

L25 ANSWER 30 OF 41 REGISTRY COPYRIGHT 2002 ACS
RN **136758-81-1** REGISTRY
CN 2-Naphthalenol, 7-[[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-, ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)
MF C19 H22 Cl N O2 . C2 H2 O4
SR CA
LC STN Files: CA, CAPLUS

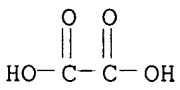
CM 1

CRN 136758-80-0
CMF C19 H22 Cl N O2



CM 2

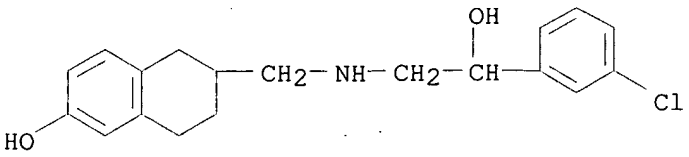
CRN 144-62-7
CMF C2 H2 O4



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 115:207684

L25 ANSWER 35 OF 41 REGISTRY COPYRIGHT 2002 ACS
RN **136758-76-4** REGISTRY
CN 2-Naphthalenol, 6-[[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)
MF C19 H22 Cl N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS



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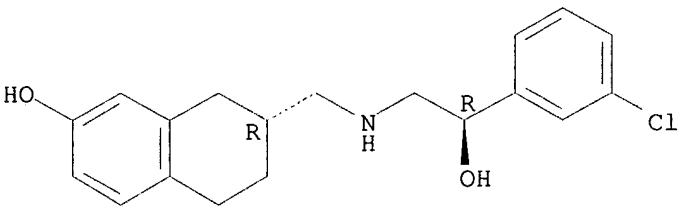
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 115:207684

L25 ANSWER 40 OF 41 REGISTRY COPYRIGHT 2002 ACS
RN **136758-71-9** REGISTRY
CN 2-Naphthalenol, 7-[[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]methyl]-5,6,7,8-tetrahydro-, hydrochloride, [R-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H22 Cl N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS
CRN (136759-07-4)

Absolute stereochemistry.



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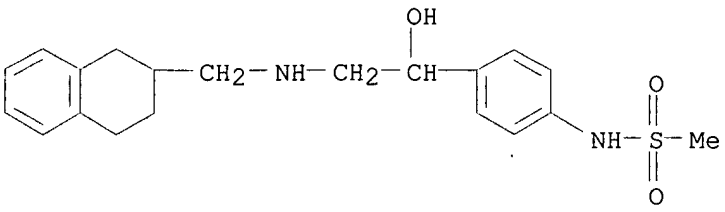
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 115:207684

L25 ANSWER 41 OF 41 REGISTRY COPYRIGHT 2002 ACS
RN **129280-12-2** REGISTRY
CN Methanesulfonamide, N-[4-[1-hydroxy-2-[[(1,2,3,4-tetrahydro-2-naphthalenyl)methyl]amino]ethyl]phenyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C20 H26 N2 O3 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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L3             STR
L4   (       237)SEA FILE=REGISTRY SUB=L2 SSS FUL L3
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L8           240 S L6 FUL
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L12           11 S L10 AND (63 OR 1)/SC,SX
L13           15 S L11,L12
L14           11 S L10 AND L13
L15            1 S L10 NOT L14

     FILE 'REGISTRY' ENTERED AT 11:03:30 ON 13 OCT 2002

     FILE 'HCAPLUS' ENTERED AT 11:03:37 ON 13 OCT 2002

     FILE 'REGISTRY' ENTERED AT 11:04:08 ON 13 OCT 2002
L16            STR L6
L17           11 S L16 SAM SUB=L8
L18          196 S L16 FUL SUB=L8
               SAV L18 JKIM44531I/A
L19           44 S L8 NOT L18

     FILE 'HCAPLUS' ENTERED AT 11:06:29 ON 13 OCT 2002
L20           11 S L19
L21            7 S L20 AND (PD<=19980128 OR PRD<=19980128 OR AD<=19980128)
L22           10 S L19 (L) (THU OR BAC)/RL
L23           10 S L20  AND (1 OR 63)/SC,SX
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L24 7 S L21 AND L22,L23

FILE 'REGISTRY' ENTERED AT 11:07:24 ON 13 OCT 2002

FILE 'HCAPLUS' ENTERED AT 11:07:32 ON 13 OCT 2002

FILE 'REGISTRY' ENTERED AT 11:07:43 ON 13 OCT 2002

FILE 'HCAPLUS' ENTERED AT 11:08:05 ON 13 OCT 2002
SEL HIT RN L24

FILE 'REGISTRY' ENTERED AT 11:08:08 ON 13 OCT 2002
L25 41 S E1-E41